VERIFICATION OF TRANSLATION

I, Eiko Nomura, residing at 3-10-3, Kamiogi, Suginami-ku, Tokyo, Japan hereby certify that to the best of my knowledge and belief, the attached document is a true translation into English made by me of JP 2004-068229.

Eiko Nomura

Eiko Nomura

February 9, 2010

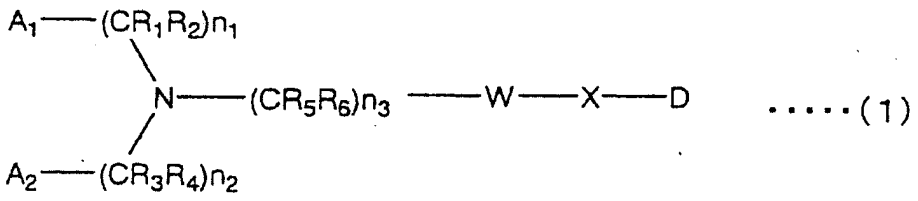
Date

[Document Name] Claims

[Claim 1]

A compound represented by the following general formula (1) or a pharmacologically acceptable salt thereof, or a prodrug thereof:

[Formula 1]



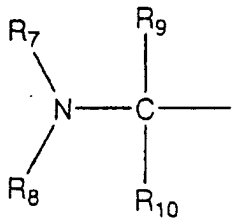
wherein

n_1, n_2, and n_3 represent an integer of 0 to 3;

R_1, R_2, R_3, R_4, R_5, and R_6 each independently represent a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, or a substitutable cyclic alkyl group having 3 to 15 carbon atoms; and

A_1 and A_2 each independently represent a hydrogen atom, a substitutable monocyclic or polycyclic heteroaromatic ring, a partly saturated substitutable polycyclic heteroaromatic ring, a substitutable monocyclic or polycyclic aromatic ring, a partially saturated substitutable polycyclic aromatic ring, a substitutable heteroring, or a group represented by the following formula (2):

[Formula 2]

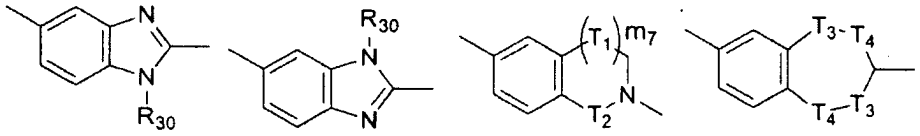


.....(2)

wherein

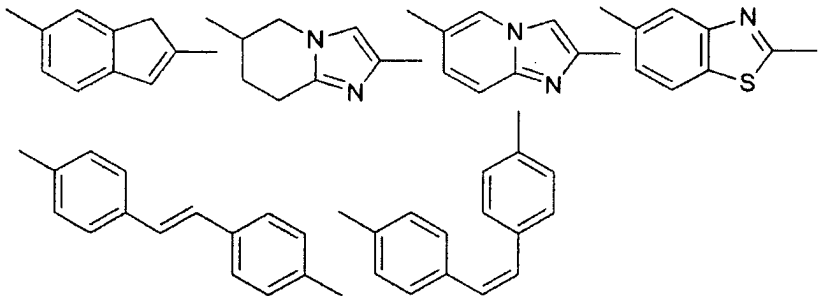
R_7, R_8, R_9, and R_{10} each independently represent a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, or a substitutable cyclic alkyl group having 3 to 15 carbon atoms; W represents any one of a substitutable benzene ring and groups represented by the following formulae (10) and (11):

[Formula 3]



.....(10)

[Formula 4]



.....(11)

wherein

R_{30} represents a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having

2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, a substitutable cyclic alkyl group having 3 to 15 carbon atoms, a methanesulfonyl group, a p-toluenesulfonyl group, a phenyl group, an acyl group, a carboxyl group, or a cyano group;

m_7 represents an integer of 0 to 2;

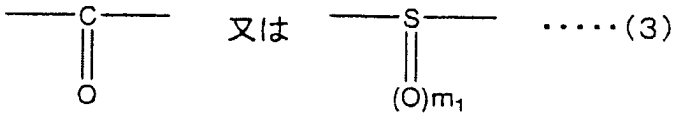
T_1 and T_2 represent CH_2 or CO;

T_3 and T_4 have a relationship of T_3 = NH and T_4 = CO, or T_3 = CO and T_4 = NH;

X represents a substitutable monocyclic or polycyclic heteroaromatic ring, a substitutable monocyclic or polycyclic aromatic ring, O, CH_2, NR_{11}, or a group represented by the following formula (3) or (12);

R_{11} represents a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, or a substitutable cyclic alkyl group having 3 to 15 carbon atoms;

[Formula 5]

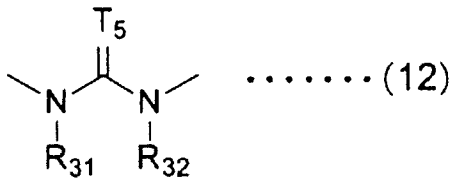


·····(3)

wherein

m_1 represents an integer of 1 or 2:

[Formula 6]



.....(12)

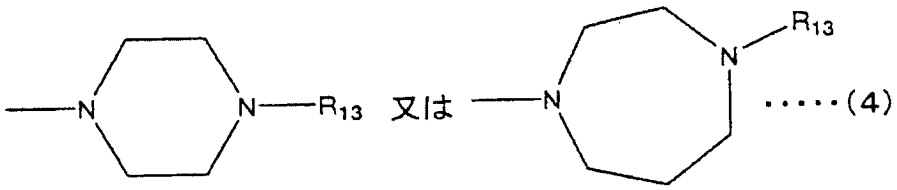
wherein

T_5 represents an oxygen atom or a sulfur atom;

R_{31} and R_{32} represent a hydrogen atom or an alkyl group having 1 to 3 carbon atoms, and R_{31} and R_{32} may be coupled to each other to form a ring;

D represents a group represented by the following formula (4) or (6):

[Formula 7]

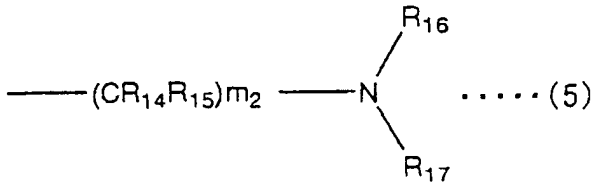


.....(4)

wherein

R_{13} represents a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, a substitutable cyclic alkyl group having 3 to 15 carbon atoms, or a group represented by the following formula (5):

[Formula 8]



wherein

m_2 represents an integer of 2 to 4;

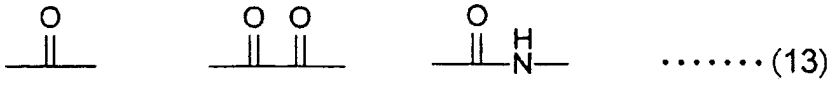
R_{14}, R_{15}, R_{16}, and R_{17} each independently represent a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, or a substitutable cyclic alkyl group having 3 to 15 carbon atoms:

[Formula 9]

wherein

Q represents a single bond when X is O, a single bond or a group represented by the formula (3) when X is NR_{11}, or a single bond, S, O, or NR_{12}, any one of the groups represented by the formula (13) when X is a substitutable monocyclic or polycyclic heteroaromatic ring, a substitutable monocyclic or polycyclic aromatic ring, CH_2 or is represented by the formula (3) or (12):

[Formula 10]

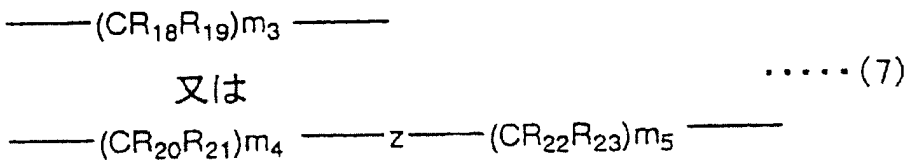


R_{12} represents a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having

2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, a substitutable cyclic alkyl group having 3 to 15 carbon atoms, a methanesulfonyl group, a p-toluenesulfonyl group, a phenyl group, an acyl group, a carboxyl group, a cyano group:

Y represents a group represented by the following formula (7):

[Formula 11]



.....(7)

wherein

m_3 represents an integer of 0 to 6;

R_{18} and R_{19} each independently represent a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, a substitutable cyclic alkyl group having 3 to 15 carbon atoms, or a substitutable aromatic ring, and R_{12} and R_{18} may form a ring;

m_4 and m_5 represent an integer of 0 to 2;

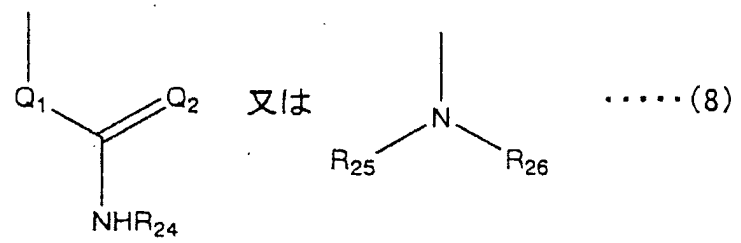
R_{20}, R_{21}, R_{22}, and R_{23} each independently represent a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, or a substitutable cyclic alkyl group having 3 to 15 carbon atoms;

z represents a substitutable cyclic alkylene group having 3 to 15 carbon atoms, a substitutable monocyclic or polycyclic heteroaromatic ring, a partly saturated substitutable polycyclic

heteroaromatic ring, a substitutable monocyclic or polycyclic aromatic ring, a partly saturated substitutable polycyclic aromatic ring, a substitutable heterocycle;

B represents any one of the groups represented by the following formulae (8) and (14):

[Formula 12]



wherein

Q_1 represents S, O, or NH and Q_2 represents S, O, or NR_{27};

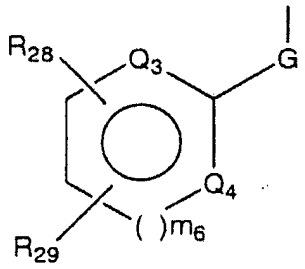
R_{24} and R_{27} each independently represent a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, a substitutable cyclic alkyl group having 3 to 15 carbon atoms, or a substitutable aromatic ring, and R_{24} and R_{27} may form a ring;

R_{25} and R_{26}, when above X is CH_2, each independently represent a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable cyclic alkyl group having 3 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms and having 1 to 3 double bonds, or a substitutable alkynyl group having 2 to 15 carbon atoms and having 1 to 3 triple bonds, and R_{25} and R_{26} may form a ring and, depending on circumstances, the ring may be formed by binding through a heteroatom, a cyclic alkyl group, an aromatic ring, a heteroaromatic ring, or a heterocycle;

R_{25} and R_{26}, when above X is not CH_2, each independently

represent a hydrogen atom, a substituent represented by the following formula (9), a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable cyclic alkyl group having 3 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms and having 1 to 3 double bonds, or a substitutable alkynyl group having 2 to 15 carbon atoms and having 1 to 3 triple bonds, and R_{25} and R_{26} may form a ring and, depending on circumstances, the ring may be formed by binding through a heteroatom, a cyclic alkyl group, an aromatic ring, a heteroaromatic ring, or a heterocycle:

[Formula 13]



.....(9)

wherein

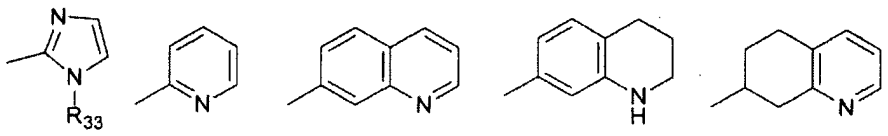
m_6 represents 0 or 1, where when m_6 = 0, Q_3 represents CH or N and Q_4 represents N, S, or O, and when m_6 = 1, Q3 and Q4 each G represents a substitutable alkylene group having 1 to 15 carbon atoms or a substitutable alkenylene group having 2 to 15 carbon atoms;

R_{28} represents an alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, an alkoxy group, a haloalkyl group, a haloalkoxy group, a hydroxyalkoxy group, a halogen atom, an amino group, an alkylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, an

alkylcarbamoyl group, a saturated heterocycle, or a heteroaromatic ring, which is substituted at any position except a nitrogen atom which may be present on the ring or may represent a hydrogen atom when $m_6 = 1$ and Q_3 and Q_2 simultaneously represent CH;

R_{29} represents a hydrogen atom or the same group as R_{24}, and may be coupled with G to form a ring:

[Formula 14]



.....(14)

wherein

R_{33} represent the same group as that of above R_{12},

wherein one or two or more asymmetric carbon atoms may exist in the compound represented by the general formula (1), where when one asymmetric carbon atom exists, the compound may be in the form of any one of a pure optically-active substance represented by the absolute configuration R or S, a mixture thereof in a predetermined ratio, and a racemic mixture thereof or when two or more asymmetric carbon atoms exist, the compound may be in the form of any one of an optically pure diastereomer, a racemic mixture thereof, and a combination thereof in a predetermined ratio.

[Claim 2]

A compound, a pharmacologically acceptable salt thereof, or a prodrug thereof according to claim 1, wherein n_1, n_2, and n_3 represent an integer of 1 and R_1, R_2, R_3, R_4, R_5, and R_6 represent a hydrogen atom.

[Claim 3]

A compound, a pharmacologically acceptable salt thereof, or a prodrug thereof according to claim 1 or 2, wherein A_1 and A_2 each independently represent a hydrogen atom or a substitutable monocyclic or polycyclic heteroaromatic ring.

[Claim 4]

A compound, a pharmacologically acceptable salt thereof, or a prodrug thereof according to any one of claims 1 to 3, wherein W represents a group represented by the formula (10).

[Claim 5]

A compound, a pharmacologically acceptable salt thereof, or a prodrug thereof according to any one of claims 1 to 3, wherein W represents a benzene ring and X represents a group represented by the formula (12).

[Claim 6]

A compound, a pharmacologically acceptable salt thereof, or a prodrug thereof according to any one of claims 1 to 3, wherein W represents a benzene ring, X represents $-CH_2-$, and D represents a group represented by the formula (6) where Q represents a group represented by NR_{12} and R_{12} is based on the same definition as described above.

[Claim 7]

A compound, a pharmacologically acceptable salt thereof, or a prodrug thereof according to any one of claims 1 to 6,

wherein D represents a group represented by the formula (6), in the formula

Q represents NR_{12} where R_{12} is based on the same definition as described above; and

Y represents a group represented by $-(CR_{18}R_{19})m_3-$ where R_{18}, R_{19}, and m_3 are based on the same definition as described above.

[Claim 8]

A compound, a pharmacologically acceptable salt thereof, or a prodrug thereof according to any one of claims 1 to 6, wherein:

D represents a group represented by the formula (6), in the formula

Q represents any one of the groups represented by the formula (13) where R_{12} is based on the same definition as described above; and

Y represents a group represented by $-(CR_{18}R_{19})m_3-$ where R_{18}, R_{19}, and m_3 are based on the same definition as described above.

[Claim 9]

A compound, a pharmacologically acceptable salt thereof, or a prodrug thereof according to any one of claims 1 to 7, wherein D represents a group represented by the formula (6) where B represents $-NR_{25}R_{26}$ where R_{25} and R_{26} are based on the same definition as described above.

[Claim 10]

A compound, a pharmacologically acceptable salt thereof, or a prodrug thereof according to any one of claims 1 to 7, wherein D represents a group represented by the formula (6) where B represents any one of the groups represented by the formula (14).

[Claim 11]

A compound, a pharmacologically acceptable salt thereof, or a prodrug thereof selected from the group consisting of:

2-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-ethanol;

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine;

[4-(6-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine;

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine;

[4-(5-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine;

4-{[N-(1H-imidazol-2-ylmethyl)-amino]-methyl-N-(4-dipropylamino-butyl)-benzamide;

2-(4-dipropylamino-butyl)-5-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-2,3-dihydro-isoindol-1-one;

2-(4-dipropylamino-butyl)-6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-2,3-dihydro-isoindol-1-one;

N-(4-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N-methyl-N',N'-dipropyl-butane-1,4-diamine;

N-methyl-N-[4-({[1-(1-methyl-1H-imidazol-2-ylmethyl)-1

H-imidazol-2-ylmethyl]-amino}-methyl)-benzyl-N',N'-dipropylbutane-1,4-diamine;

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1H-inden-2-yl)-butyl]-dipropyl-amine;

1-(4-dipropylaminobutyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-urea;

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-methyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine;

3-(3-dipropylaminopropyl)-8-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-3,4-dihydro-1H-benzo[e][1,4]diazepin-2,5-dione;

4-{[(3,5-dimethyl-pyridin-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-N-(4-dipropylaminomethyl-phenyl)-benzamide;

4-{[(5-ethyl-pyridin-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-N-(4-dipropylaminomethyl-phenyl)-benzamide;

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-3,4-dihydro-1H-isoquinolin-2-yl)-butyl]-dipropyl-amine;

[3-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-methyl-1H-benzimidazol-2-yl)-benzyl]-dipropyl-amine;

6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridine-2-carboxylic acid-(4-dipropylamino-butyl)-amide;

N-(4-dipropylamino-butyl)-4-{[(1-methyl-1H-imidazo-2-ylmethyl)-(5-methyl-pyridin-2-ylmethyl)-amino]-methyl}-benzamide;

N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-methanesulfonamide;

N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-4-methyl-benzenesulfonamide;

N-ethyl-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N',N'-dipropyl-butane-1,4-diamine;

N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N-phenyl-N',N'-dipropyl-butane-1,4-diamine;

N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-acetamide;

1-(4-dipropylamino-butyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-1-methyl-urea;

1-(4-dipropylamino-butyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-1,3-dimethyl-urea;

N-methyl-N-[4-({(1-methyl-1H-imidazol-2-ylmethyl)-[1-(toluene-4-sulfonyl)-1H-imidazol-2-ylmethyl]-amino}-methyl)-benzyl]-N",N"-dipropyl-butane-1,4-diamine;

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-methyl-1H-benzimidazol-2-yl)-b

enzyl]-dipropyl-amine;

6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-imidazo[1,2-a]pyridine-2-carboxylate-(4-dipropyl)-amino-butyl)-amide;

N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N',N'-dipropyl-N-(2,2,2-trifluoro-ethyl)-butane-1,4-diamine;

N-(4-{[(1-methanesulfonyl-1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N-methyl-N",N"-dipropyl-butane-1,4-diamine;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionitrile;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid methyl ester;

1-(4-dipropylamino-butyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-thiourea;

{3-[6-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-pyridin-2-yl]-propyl}-dipropyl-amine;

N-(4-dipropylamino-butyl)-2,2,2-trifluoro-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-acetamide;

[4-(5-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1,3-dihydro-isoindol-2-yl)-butyl]-dipropyl-amine;

{4-(1E)-[2-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-

imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-vinyl]-benzyl}-dipropyl-amine;

{[4-((1Z)-2-{4-[(dipropylamino)-methyl]-phenyl}-vinyl)-phenyl]-methyl}-(imidazol-2-ylmethyl)-[(1-methylimidazol-2-yl)-methyl]-amine;

{[4-((1E)-2-{4-[2-(dipropylamino)-ethyl]-phenyl}-vinyl)-phenyl]-methyl}-(imidazol-2-ylmethyl)-[(1-methylimidazol-2-yl)-methyl]-amine;

{[4-((1E)-2-{4-[(dipropylamino)-methyl]-phenyl}-vinyl)-phenyl]-methyl}-bis-(imidazol-2-ylmethyl)-amine;

[4-(6-{[(1H-imidazol-2-yl-methyl)-(1-methyl-imidazol-2-yl-methyl)-amino]-methyl}-benzothiazol-2-yl)-benzyl]-dipropyl-amine;

(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-methyl-(4-piperidin-1-ylbutyl)amine;

2-(2-(4-dipropylamino-butyl)-6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzimidazol-1-yl)-ethanol;

[3-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-propyl]-dipropyl-amine;

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-isopropyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine;

[5-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-pentyl]-dipropyl-amine;

N-(4-{[(1H-imidazol-2-ylmethyl)-(5,6,7,8-tetrahydrohyd

ro-quinolin-8-yl)-amino]-methyl}-benzyl)-N-methyl-N',N'-dipropyl-butane-1,4-diamine;

N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(5,6,7,8-tetrahydro-quinolin-8-yl)-amino]-methyl}-benzyl)-methanesulfonamide;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid;

(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-cyanamide;

(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-formamide;

[(4-{[(1-carboxymethyl-1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)amino]-acetic acid; and

[4-(1-benzyl-6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine.

[Claim 12]

A compound, a pharmacologically acceptable salt thereof, or a pro-drug thereof selected from the group consisting of:

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid ethyl ester;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-

amino]-propionic acid isopropyl ester;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid benzyl ester;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid butyl ester;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid-5-methyl-2-oxo-[1,3]-dioxol-4-ylmethyl ester;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid-1-ethyl-propoxycarbonyloxy methyl ester;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid-1-(cyclohexyloxycarbonyloxy)-ethyl ester;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid-methoxycarbonyloxy methyl ester;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid-ethoxycarbonyloxy methyl ester;

2,2-dimethyl-propionic acid-3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionyloxy methyl ester;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethy

l)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid-3-oxo-1,3-dihydro-isobenzofuran-1-yl ester;

Hexanoic acid-3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionyloxymethyl ester;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid-3-cyclopentyl-propionyloxymethyl ester;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid-diethylcarbamoyloxy methyl ester;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid t-butoxycarbonyl methyl ester;

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-N-ethyl-propionamide;

3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-propionic acid;

3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-propionate;

3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-propionic acid-5-methyl-2-oxo-[1,3]dioxol-4-ylmethyl ester;

3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-propionic acid-1-(cyclohexyloxycarbonyloxy)-ethyl ester;

2,2-dimethyl-propionic acid-3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-propionyloxymethyl ester;

3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-propionic acid-3-oxo-1,3-dihydro-isobenzofuran-1-yl ester;

3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-propionic acid-diethylcarbamoyloxy methyl ester; and

3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-N-ethyl-propionamide.

[Claim 13]

A medical composition, comprising as an active ingredient the compound, the pharmacologically acceptable salt thereof, or the prodrug thereof according to any one of claims 1 to 12.

[Claim 14]

A CXCR4 antagonist, comprising as an active ingredient the compound, the pharmacologically acceptable salt thereof, or the prodrug thereof according to any one of claims 1 to 12.

[Claim 15]

An antiviral drug, comprising as an active ingredient the compound, the pharmacologically acceptable salt thereof, or the prodrug thereof according to any one of claims 1 to 12.

[Claim 16]

A rheumatic disease ameliorating agent based on a CXCR4

antagonism, comprising as an active ingredient the compound, the pharmacologically acceptable salt thereof, or the prodrug thereof according to any one of claims 1 to 12.

[Claim 17]

A cancer metastatic disease ameliorating agent based on a CXCR4 antagonism, comprising as an active ingredient the compound, the pharmacologically acceptable salt thereof, or the prodrug thereof according to any one of claims 1 to 12.

[Document name] Specification

[Title of the invention] AMINE-BASED BASIC COMPOUND AND USE THEREOF

[Technical Field]

[0001]

The present invention relates to an amine compound or a pharmacologically acceptable salt thereof, or a prodrug thereof, in particular, an amine compound having anti-virus activity based on antagonism against a chemokine receptor CXCR4. Furthermore, the present invention relates to a therapeutical drug including the above-mentioned compounds as active ingredients for associated diseases such as rheumatic diseases and cancer metastatic diseases, particularly based on antagonism against the chemokine receptor CXCR4.

[Background Art]

[0002]

Examples of therapeutic drugs against the acquired immunodeficiency syndrome (AIDS) caused by an infection with the human immunodeficiency virus (HIV) include a reverse transcriptase inhibitor and a protease inhibitor. However, therapeutic effectiveness of those drugs has been lost due to the emergence of drug resistant HIV mutants (see, for example, Non-patent Document 1). Also, the polypharmacy using the combination of such drugs has such disadvantages that it requires many conditions to be observed in administration, that it is complex, that it needs many kinds of drugs to be administered, and that it causes various side effects (see, for example,

Non-patent Document 2). Moreover, particularly in case of using the protease inhibitor, it is known that the probability of causing emergence and screening of the resistant strain will increase unless the administration of approximately 100% of the drugs is kept, in spite of the complex administration method and many side effects thereof (see, for example, Non-patent Document 3).

[0003]

Alternatively, development of vaccine has been attempted because many viral diseases were destroyed or remarkably weakened by vaccines in the past. However, this is considered to be extremely difficult since mutations are occurred frequently in HIV (see, for example, Non-patent Document 4).

[0004]

Although several kinds of compounds having an anti-HIV effect have been reported as described above,
it is now strongly desired to develop a novel antiviral drug which has excellent anti-retrovirus effect, is capable of opposing to the expression of the resistance, and which has little toxicity and causes little side effect, thereby allowing a long term administration.

[0005]

Chemokine is one kind of cytokine which renders chemotaxis to leukocytes, and is a secretory protein. Chemokine is classified into CXC-chemokine, CC-chemokine, C-chemokine, CX3C-chemokine according to the cysteine (Cys) sequence at N-terminal, and the total number thereof is said to be about 30. The chemokine receptor includes several sub-types. Among them, it is known that the CXCR4 to which a ligand CXC-chemokine SDF-1α binds is utilized as a coreceptor on infection to a host cell

of a T cell-directive HIV (see, for example, Non-patent Document 5 and Non-patent Document 6). The HIV invades through binding of its envelope protein gp120 to the CXCR4 on the surface of a host cell. That is, the drug having antagonism against the CXCR4 is expected as an anti-HIV drug based on a novel mechanism of invasion inhibition, and there have been reported three low-molecular compounds as such drugs: AMD3100 (see, for example, Non-patent Document 7), T22 (see, for example, Non-patent Document 8), and ALX40-4C (see, for example, Non-patent Document 9).

[0006]

On the other hand, it has been elucidated that the CXCR4 associates with various diseases besides HIV infection. For example, there has been reported its association with a rheumatic disease (see, for example, Patent Document 1), a cancer metastatic disease (see, for example, Non-patent Document 10), or the like.

[0007]

As a therapeutic drug for such diseases, it is strongly desired to develop a novel low-molecular drug which has CXCR4 antagonism, and which has little toxicity and causes little side effect, thereby allowing a long-term administration.

[Patent Document 1] WO 00/06086

[Non-patent Document 1] Saishin Igaku, Vol. 53, No. 9, p. 2031 (1998)

[Non-patent Document 2] Nikkei Science, Oct., p. 29 (1998)

[Non-patent Document 3] Molecular Medicine, Vol. 36, No. 9, p. 1012 (1999)

[Non-patent Document 4] Nikkei Science, Oct., p. 42 (1998)

[Non-patent Document 5] Science, 272, 872 (1996)

[Non-patent Document 6] Nature, 382, 829 (1996)

[Non-patent Document 7] J. Exp. Med, 186, 1383 (1997)

[Non-patent Document 8] J. Exp. Med, 186, 1389 (1997)

[Non-patent Document 9] J. Exp. Med, 186, 1395 (1997)

[Non-patent Document 10] Nature, 410, 50 (2001)

[Disclosure of the Invention]

[Problems to be solved by the Invention]

[0008]

An object of the present invention is to provide a drug and a prodrug thereof having an excellent anti-retrovirus effect, and also a novel chemical structure having an excellent CXCR4 antagonism against SDF-1α, and high safety.

[0009]

As a result of studies to develop a compound having an excellent anti-retrovirus effect, and also having a novel chemical structure useful as an excellent CXCR4 antagonist against SDF-1α, the inventors of the present invention have found a group of amine compounds which exhibit protection characteristics in a cell vaccinated with HIV-1 and therefore are regarded as having a potentiality for treatments of AIDS, AIDS-associated complication, and the like, and which also exhibit a powerful CXCR4 antagonism and therefore are regarded as having a potentiality for treatments of rheumatic disease, cancer metastatic diseases, and the like. The group of amine compounds has been applied for a patent (PCT/JP 03/11381), after that, the inventors of the present invention have found a more useful compound thereafter. Thus, another object of the present invention is to provide a compound represented by the general formula (1) defined below, which has an anti-virus activity for

mainly HIV and a CXCR4 antagonism, and the present invention is to provide a drug composed of the compound represented by the general formula (1), for treating virus-infected patients and patients suffering from rheumatism, cancer, or the like.

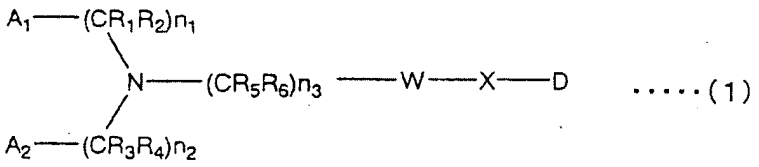
[Means for solving the Problems]

[0010]

The present invention relates to a compound represented by the following general formula (1), a pharmacologically acceptable salt thereof, or a prodrug thereof:

[0011]

[Formula 15]



[0012]

where

n_1, n_2, and n_3 each represent an integer of 0 to 3;

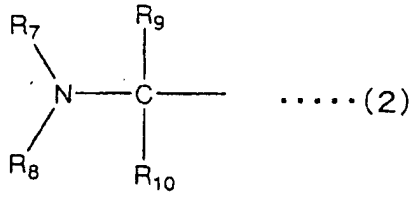
R_1, R_2, R_3, R_4, R_5, and R_6 each independently represent a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, or a substitutable cyclic alkyl group having 3 to 15 carbon atoms; and

A_1 and A_2 each independently represent a hydrogen atom, a substitutable monocyclic or polycyclic heteroaromatic ring, a partly saturated substitutable polycyclic heteroaromatic ring, a substitutable monocyclic or polycyclic aromatic ring, a partly

saturated substitutable polycyclic aromatic ring, a substitutable heterocycle, or a group represented by the following formula (2):

[0013]

[Formula 16]



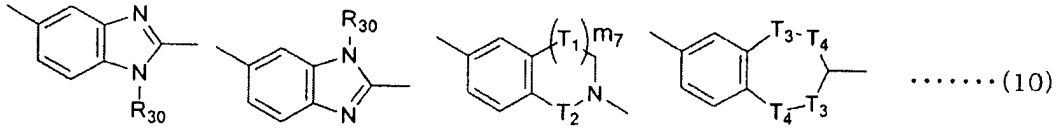
[0014]

where

R_7, R_8, R_9, and R_{10} each independently represent a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, or a substitutable cyclic alkyl group having 3 to 15 carbon atoms;

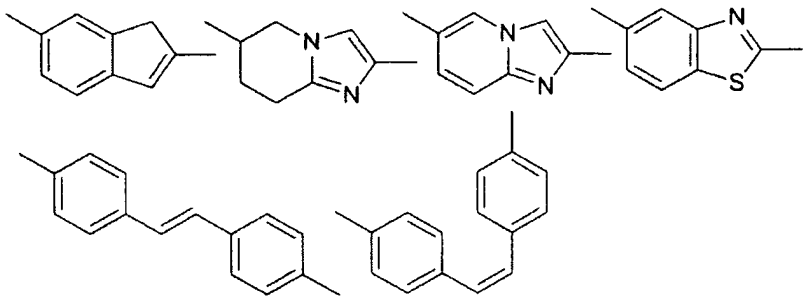
W represents any one of a substitutable benzene ring and groups represented by the following formulae (10) and (11);

[Formula 17]



[0015]

[Formula 18]



.....(11)

[0016]

where

R_{30} represents a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, or a substitutable cyclic alkyl group having 3 to 15 carbon atoms, a methanesulfonyl group, a p-toluenesulfonyl group, a phenyl group, an acyl group, a carboxyl group, or a cyano group;

m_7 represents an integer of 0 to 2;

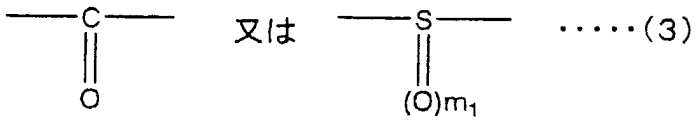
T_1 and T_2 represent CH_2 or CO;

T_3 and T_4 have a relationship of T_3 = NH and T_4 = CO, or T_3 = CO and T_4 = NH;

X represents a substitutable monocyclic or polycyclic heteroaromatic ring, a substitutable monocyclic or polycyclic aromatic ring, O, CH_2, NR_{11}, or a group represented by the following formula (3) or (12);

R_{11} represents a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, or a substitutable cyclic alkyl group having 3 to 15 carbon atoms;

[Formula 19]

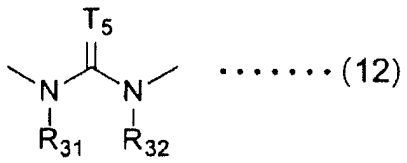


wherein

m_1 represents an integer of 1 or 2:

[0017]

[Formula 20]



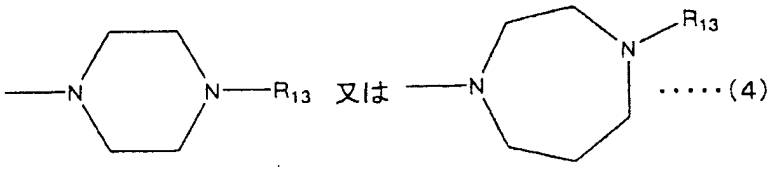
where

T_5 represents an oxygen atom or a sulfur atom;

R_{31} and R_{32} represent a hydrogen atom or an alkyl group having 1 to 3 carbon atoms, and R_{31} and R_{32} may be coupled to each other to form a ring;

[0018]

[Formula 21]



D represents a group represented by the above formula (4) or the following formula (6),

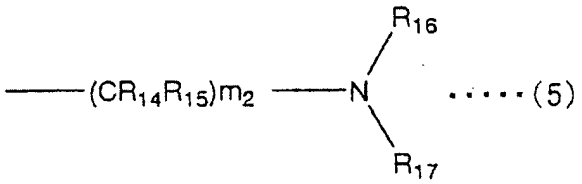
in the formula (4),

R_{13} represents a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having

2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, a substitutable cyclic alkyl group having 3 to 15 carbon atoms, or a group represented by the following formula (5):

[0019]

[Formula 22]



where

m_2 represents an integer of 2 to 4;

R_{14}, R_{15}, R_{16}, and R_{17} each independently represent a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, or a substitutable cyclic alkyl group having 3 to 15 carbon atoms;

[0020]

[Formula 23]

where

Q represents a single bond when X is O, a single bond or a group represented by the formula (3) when X is NR_{11}, or a single bond, S, O, or NR_{12}, any one of the groups represented by the formula (13) when X is a substitutable monocyclic or polycyclic heteroaromatic ring, a substitutable monocyclic or polycyclic aromatic ring, CH_2 or is represented by the formula (3) or (12);

[0021]

[Formula 24]

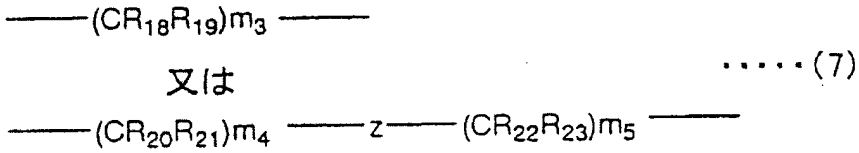
.....(13)

R_{12} represents a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, a substitutable cyclic alkyl group having 3 to 15 carbon atoms, a methanesulfonyl group, a p-toluenesulfonyl group, a phenyl group, an acyl group, a carboxyl group, a cyano group;

Y represents a group represented by the following formula (7):

[0022]

[Formula 25]



.....(7)

where

m_3 represents an integer of 0 to 6;

R_{18} and R_{19} each independently represent a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, a substitutable cyclic alkyl group having 3 to 15 carbon atoms, or a substitutable aromatic ring, and R_{12} and R_{18} may form a ring;

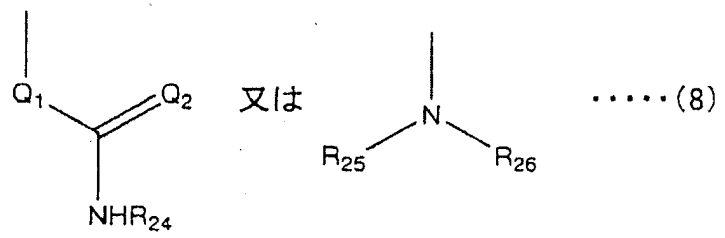
m_4 and m_5 represent an integer of 0 to 2;

R_{20}, R_{21}, R_{22}, and R_{23} each independently represent a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, or a substitutable cyclic alkyl group having 3 to 15 carbon atoms;

z represents a substitutable cyclic alkylene group having 3 to 15 carbon atoms, a substitutable monocyclic or polycyclic heteroaromatic ring, a partly saturated substitutable polycyclic heteroaromatic ring, a substitutable monocyclic or polycyclic aromatic ring, a partly saturated substitutable polycyclic aromatic ring, a substitutable heterocycle;

[0023]

[Formula 26]



.....(8)

B represents any one of the groups represented by the above formula (8) and formula (14):

in the formula (8),

Q_1 represents S, O, or NH and Q_2 represents S, O, or NR_{27};

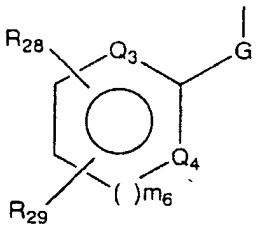
R_{24} and R_{27} each independently represent a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, a substitutable cyclic alkyl group having 3 to 15 carbon atoms, or a substitutable aromatic ring, and R_{24} and R_{27} may form a ring;

R_{25} and R_{26}, when above X is CH_2, each independently represent

a hydrogen atom, a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable cyclic alkyl group having 3 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms and having 1 to 3 double bonds, or a substitutable alkynyl group having 2 to 15 carbon atoms and having 1 to 3 triple bonds, and R_{25} and R_{26} may form a ring and, depending on circumstances, the ring may be formed by binding through a heteroatom, a cyclic alkyl group, an aromatic ring, a heteroaromatic ring, or a heterocycle;

R_{25} and R_{26}, when above X is not CH_2, each independently represent a hydrogen atom, a substituent represented by the following formula (9), a substitutable alkyl group having 1 to 15 carbon atoms, a substitutable cyclic alkyl group having 3 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms and having 1 to 3 double bonds, or a substitutable alkynyl group having 2 to 15 carbon atoms and having 1 to 3 triple bonds, and R_{25} and R_{26} may form a ring and, depending on circumstances, the ring may be formed by binding through a heteroatom, a cyclic alkyl group, an aromatic ring, a heteroaromatic ring, or a heterocycle:

[Formula 27]



.....(9)

where

m_6 is 0 or 1, where when m_6 = 0, Q_3 represents CH or N and Q_4 represents N, S, or O, and when m_6 = 1, Q3 and Q4 each

independently represent CH or N;

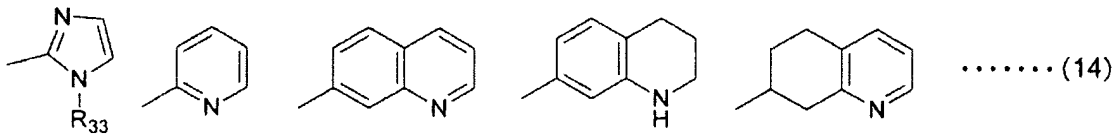
G represents a substitutable alkylene group having 1 to 15 carbon atoms or a substitutable alkenylene group having 2 to 15 carbon atoms;

R_{28} represents an alkyl group having 1 to 15 carbon atoms, a substitutable alkenyl group having 2 to 15 carbon atoms, a substitutable alkynyl group having 2 to 15 carbon atoms, an alkoxy group, a haloalkyl group, a haloalkoxy group, a hydroxyalkoxy group, a halogen atom, an amino group, an alkylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, an alkylcarbamoyl group, a saturated heterocycle, or a heteroaromatic ring, which is substituted at any position except a nitrogen atom which may be present on the ring or may represent a hydrogen atom when $m_6 = 1$ and Q_3 and Q_2 simultaneously represent CH;

R_{29} represents a hydrogen atom or the same group as R_{24}, and may be coupled with G to form a ring.

[0024]

[Formula 28]



.....(14)

where

R_{33} represent the same group as that of R_{12}.

Further, one or two or more asymmetric carbon atoms may exist in the compound represented by the general formula (1), where when one asymmetric carbon atom exists, the compound may be in the form of any one of a pure optically-active substance

represented by the absolute configuration R or S, a mixture thereof in a predetermined ratio, and a racemic mixture thereof or when two or more asymmetric carbon atoms exist, the compound may be in the form of any one of an optically pure diastereomer, a racemic mixture thereof, and a combination thereof in an predetermined ratio.

The terms as used in this specification are defined as described below, and they may be used singly or in combination.

An alkyl group represents a saturated hydrocarbon group with any structure of a linear chain, a branched chain, or a ring. Examples of the alkyl group include a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, an isobutyl group, a pentyl group, and a neopentyl group.

An alkenyl group represents a hydrocarbon group with any structure of a linear chain, a branched chain, or a ring having a double bond. Examples of the alkenyl group include an allyl group, a 1-butenyl group, a 2-butenyl group, an isobutenyl group, and a cyclohexenyl group.

An alkynyl group represents a hydrocarbon group with any structure of a linear chain, a branched chain, or a ring having a triple bond. Examples of the alkynyl group include a propynyl group and a 1-butynyl group.

A cyclic alkyl group represents a cyclic hydrocarbon group. Examples of the cyclic alkyl group include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, and a cycloheptyl group.

An aromatic ring represents an aromatic ring formed of a hydrocarbon. Examples of a monocyclic aromatic ring include a benzene ring; and examples of a polycyclic aromatic ring include

a naphthalene ring and an anthracene ring. Examples of a partly saturated polycyclic aromatic ring include a dihydronaphthalene ring, a tetralin ring, an indan ring and the like. A heteroaromatic ring represents an aromatic ring having one or two or more nitrogen atoms, oxygen atoms, or sulfur atoms in the ring. Examples of a monocyclic heteroaromatic ring include a pyrrole ring, a furan ring, a thiophene ring, a pyridine ring, a pyrimidine ring, a pyridazine ring, a pyrazine ring, an imidazole ring, a pyrazole ring, an oxazole ring, a thiazole ring, a thiadiazole ring, an oxadiazole ring, and a triazole ring. Examples of a polycyclic heteroaromatic ring include a quinoline ring, an isoquinoline ring, a benzimidazole ring, an indazole ring, a benzothiazole ring, a benzoxazole ring, an indole ring, a benzofuran ring, and a benzothiophene ring.

Examples of a partly saturated polycyclic aromatic ring include a tetrahydroisoquinoline ring and a tetrahydroquinoline ring. A heterocycle represents a saturated ring that may have one or two or more nitrogen atoms, oxygen atoms, or sulfur atoms in the ring. Examples of the heterocycle include pyrrolidine, piperidine, piperazine, morpholine, and thiomorpholine.

An alkylene group represents a hydrocarbon group that can be bonded to two groups at the terminals. Examples of the alkylene group include an ethylene group, a propylene group, an isopropylene group, a butylene group, an isobutylene group, and a 2,2-dimethylethylene group.

An alkenylene group represents an alkylene group having a double bond. Examples of the alkenylene group include a propenylene group, a 2-butenylene group, and a 1,3-butadienylene group.

An alkynylene group represents an alkylene group having a triple bond. Examples of the alkynylene group include a propynylene group and a butynylene group.

An acyl group is group to which a hydrogen atom, an alkyl group, a monocyclic or polycyclic heteroaromatic ring or monocycle or a polycyclic aromatic ring bonds through a carbonyl group. These groups each may substitute at any position. Examples of the acyl group include a formyl group, an acetyl group, a benzoyl group, and a trifluoroacetyl group.

B represents $R_{25}(R_{26})N-$, where R_{25} and R_{26} may form a ring. Examples of a ring formed by binding R_{25} and R_{26} directly together with a nitrogen atom to which they are bound include a pyrrolidine ring, a piperidine ring, a hexamethyleneimine ring, and a heptamethyleneimine ring. Examples of a ring formed by binding R_{25} and R_{26} through a heteroatom together with a nitrogen atom to which they are bound include a morpholine ring and a piperazine ring. Examples of a ring formed by binding R_{25} and R_{26} through an aromatic ring together with a nitrogen atom to which they are bound include a tetrahydroisoquinoline ring and a tetrahydroindole ring.

When R_{25} and/or R_{26} is a group represented by the formula (8) and R_{29} and G in the formula form a ring, examples of R_{25} and R_{26} include a tetralinyl group, an indanyl group, a tetrahydroquinolyl group, and a tetrahydroisoquinolyl group.

The term "substitutable" in the expressions for each substituent means to be substituted with a hydroxyl group, a thiol group, a formyl group, a carboxyl group, a sulfonyl group, an amino group, an amide group, a carbamoyl group, a cyano group, an alkoxy group, an alkoxycarbonyl group, an alkylamino group,

an acylamino group, an alkoxycarbonylamino group, alkylthio group, an aminosulfonyl group, a dialkylaminosulfonyl group, a methanesulfonyl group, a p-toluenesulfonyl group, a phenyl group, phthalidyloxycarbonyl group, a halogen atom, or the like. Here, the alkoxy group represents a group in which a substitutable alkyl group binds through an oxygen atom. The acylamino group represents a group in which an alkyl group or a phenyl group binds to an amino group through a carbonyl group. Further, examples of the "substitutable" groups in A_1 and A_2 include an alkyl group, a hydroxyalkyl group, an alkoxyalkyl group, an aminoalkyl group, an aryl group, and heteroaryl group other than the group described above.

The prodrug is a precursor substance that becomes an effective drug through chemical or biochemical metabolism after administration to the living body. Specifically, the prodrug is a compound which is obtained by binding one or more appropriate groups, that is eliminated by metabolism in the living body, such as alkoxycarbonyl group or dialkylaminosulfone group with N in the ring or chain of a heterocycle or the like contained in the compound represented by the general formula (1). Alternatively, the prodrug is a compound coupled with one or more ester groups, amide groups, or the like that utilize alcohol or carboxylic acid, which may be contained in the compound represented by the general formula (1).

In addition, examples of a pharmacologically acceptable salt include trifluoroacetates, hydrochlorides, acetates, sulfates, nitrates, lactates, maleates, methanesulfonates, toluenesulfonates, tartrates, citrates, oxalates, malonates, succinates, fumarates, propionates, butyrates, glucuronic acid,

terephthalic acid, and phosphoric acid.

[0025]

The following compounds can be exemplified as the amine compound of the present invention:

2-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-ethanol [Compound No. 1]

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 2]

[4-(6-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 3]

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 4]

[4-(5-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 5]

4-{[N-(1H-imidazol-2-ylmethyl)-amino]-methyl-N-(4-dipropylamino-butyl)-benzamide [Compound No. 6]

2-(4-dipropylamino-butyl)-5-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-2,3-dihydro-isoindol-1-one [Compound No. 7]

2-(4-dipropylamino-butyl)-6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-2,3-dihydro-isoindol-1-one [Compound No. 8]

N-(4-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N-methyl-N',N'-dipropyl-butane-1,4-diamine [Compound No. 9]

N-methyl-N-[4-({[1-(1-methyl-1H-imidazol-2-ylmethyl)-1H-imidazol-2-ylmethyl]-amino}-methyl)-benzyl-N',N'-dipropylbutane-1,4-diamine [Compound No. 10]

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1H-inden-2-yl)-butyl]-dipropyl-amine [Compound No. 11]

1-(4-dipropylaminobutyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-urea [Compound No. 12]

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-methyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 13]

3-(3-dipropylaminopropyl)-8-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-3,4-dihydro-1H-benzo[e][1,4]diazepin-2,5-dione [Compound No. 14]

4-{[(3,5-dimethyl-pyridin-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-N-(4-dipropylaminomethyl-phenyl)-benzamide [Compound No. 15]

4-{[(5-ethyl-pyridin-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-N-(4-dipropylaminomethyl-phenyl)-benzamide [Compound No. 16]

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-3,4-dihydro-1H-isoquinolin-2-yl)-butyl]-dipropyl-amine [Compound No. 17]

[3-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-methyl-1H-benzimidazol-2-yl)-benzyl]-dipropyl-amine [Compound No. 18]

6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-5,6,7,8-tetrahydro-imidazo[1,2-a]pyr

idin-2-carboxylic acid-(4-dipropylamino-butyl)-amide [Compound No. 19]

N-(4-dipropylamino-butyl)-4-{[(1-methyl-1H-imidazo-2-ylmethyl)-(5-methyl-pyridin-2-ylmethyl)-amino]-methyl}-benzamide [Compound No. 20]

N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-methanesulfonamide [Compound No. 21]

N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-4-methyl-benzenesulfonamide [Compound No. 22]

N-ethyl-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N',N'-dipropyl-butane-1,4-diamine [Compound No. 23]

N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N-phenyl-N',N'-dipropyl-butane-1,4-diamine [Compound No. 24]

N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-acetamide [Compound No. 25]

1-(4-dipropylamino-butyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-1-methyl-urea [Compound No. 26]

1-(4-dipropylamino-butyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-1,3-dimethyl-urea [Compound No. 27]

N-methyl-N-[4-({(1-methyl-1H-imidazol-2-ylmethyl)-[1-(toluene-4-sulfonyl)-1H-imidazol-2-ylmethyl]-amino}-methyl)-benzyl]-N",N"-dipropyl-butane-1,4-diamine [Compound No. 28]

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-methyl-1H-benzimidazol-2-yl)-benzyl]-dipropyl-amine [Compound No. 29]

6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-imidazo[1,2-a]pyridine-2-carboxylic acid-(4-dipropyl)-amino-butyl)-amide [Compound No. 30]

N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N',N'-dipropyl-N-(2,2,2-trifluoro-ethyl)-butane-1,4-diamine [Compound No. 31]

N-(4-{[(1-methanesulfonyl-1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N-methyl-N",N"-dipropyl-butane-1,4-diamine [Compound No. 32]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionitrile [Compound No. 33]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid methyl ester [Compound No. 34]

1-(4-dipropylamino-butyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-thiourea [Compound No. 35]

{3-[6-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-pyridin-2-yl]-propyl}-dipropyl-amine [Compound No. 36]

N-(4-dipropylamino-butyl)-2,2,2-trifluoro-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-acetamide [Compound No. 37]

[4-(5-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1,3-dihydro-isoindol-2-yl)-butyl

]-dipropyl-amine [Compound No. 38]

{4-(1E)-[2-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-vinyl]-benzyl}-dipropyl-amine [Compound No. 39]

{[4-((1Z)-2-{4-[(dipropylamino)-methyl]-phenyl}-vinyl)-phenyl]-methyl}-(imidazol-2-ylmethyl)-[(1-methylimidazol-2-yl)-methyl]-amine [Compound No. 40]

{[4-((1E)-2-{4-[2-(dipropylamino)-ethyl]-phenyl}-vinyl)-phenyl]-methyl}-(imidazol-2-ylmethyl)-[(1-methylimidazol-2-yl)-methyl]-amine [Compound No. 41]

{[4-((1E)-2-{4-[(dipropylamino)-methyl]-phenyl}-vinyl)-phenyl]-methyl}-bis-(imidazol-2-ylmethyl)-amine [Compound No. 42]

[4-(6-{[(1H-imidazol-2-yl-methyl)-(1-methyl-imidazol-2-yl-methyl)-amino]-methyl}-benzothiazol-2-yl)-benzyl]-dipropyl-amine [Compound No. 43]

(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-methyl-(4-piperidin-1-ylbutyl)amine [Compound No. 44]

2-(2-(4-dipropylamino-butyl)-6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzimidazol-1-yl)-ethanol [Compound No. 45]

[3-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-propyl]-dipropyl-amine [Compound No. 46]

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-isopropyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 47]

[5-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol

-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-pentyl]-dipropyl-amine [Compound No. 48]

N-(4-{[(1H-imidazol-2-ylmethyl)-(5,6,7,8-tetrahydrohydro-quinolin-8-yl)-amino]-methyl}-benzyl)-N-methyl-N',N'-dipropyl-butane-1,4-diamine [Compound No. 49]

N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(5,6,7,8-tetrahydro-quinolin-8-yl)-amino]-methyl}-benzyl)-methanesulfonamide [Compound No. 50]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid [Compound No. 51]

(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-cyanamide [Compound No. 52]

(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-formamide [Compound No. 53]

[(4-{[(1-carboxymethyl-1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)amino]-acetic acid [Compound No. 54]

[4-(1-benzyl-6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 55]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid ethyl ester [Compound No. 56]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid isopropyl ester [Compound No. 57]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid benzyl ester [Compound No. 58]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid butyl ester [Compound No. 59]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid-5-methyl-2-oxo-[1,3]-dioxol-4-ylmethyl ester [Compound No. 60]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid-1-ethyl-propoxycarbonyloxy methyl ester [Compound No. 61]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid-1-cyclohexyloxycarbonyloxy-ethyl ester [Compound No. 62]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid-methoxycarbonyloxy methyl ester [Compound No. 63]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid-ethoxycarbonyloxy methyl ester [Compound No. 64]

2,2-dimethyl-propionic acid-3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-a

mino]-propionyloxy methyl ester [Compound No. 65]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid-3-oxo-1,3-dihydro-isobenzofuran-1-yl ester [Compound No. 66]

Hexanoic acid-3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionyloxymethyl ester [Compound No. 67]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid-3-cyclopentyl-propionyloxymethyl ester [Compound No. 68]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid diethylcarbamoyloxymethyl ester [Compound No. 69]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid t-butoxycarbonylmethyl ester [Compound No. 70]

3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-N-ethyl-propionamide [Compound No. 71]

3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-propionic acid [Compound No. 72]

3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-propionate [Compound No.

73]

3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-propionic acid-5-methyl-2-oxo-[1,3]dioxol-4-ylmethyl ester [Compound No. 74]

3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-propionic acid-1-cyclohexyloxycarbonyloxy-ethyl ester [Compound No. 75]

2,2-dimethyl-propionic acid-3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-propionyloxymethyl ester [Compound No. 76]

3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-propionic acid-3-oxo-1,3-dihydro-isobenzofuran-1-yl ester [Compound No. 77]

3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-propionic acid diethylcarbamoyloxymethyl ester [Compound No. 78]

3-[(4-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)-amino]-N-ethyl-propionamide [Compound No. 79]

The present invention relates to a CXCR4 antagonist including the above-mentioned compounds or a pharmaceutically acceptable salt thereof as an active ingredient.

[0026]

The CXCR4 antagonist or salt thereof according to the present invention may be used in treatment or prevention of a viral disease

such as AIDS, cancer treatment, or treatment or prevention of rheumatism, etc.

[0027]

The pharmacologically acceptable salt is a salt which may be formed by the amine compound represented by the above described formula (1), and may be any salt that is pharmacologically acceptable. For example, trifluoroacetates, hydrochlorides, acetates, sulfates, nitrates, lactates, maleates, methanesulfonates, toluenesulfonates, tartrates, citrates, oxalates, malonates, succinates, fumarates, propionates, butyrates, glucuronic acid, terephthalic acid, phosphoric acid and the like can be given. Those compounds may form a hydrate or a solvate.

[0028]

One or two or more asymmetric carbon atoms may exist in the compound represented by the general formula (1). When one asymmetric carbon atoms exists, the compound may be in any form of a pure optically-active substance represented as absolute configuration of R or S, a mixture thereof in an arbitrary ratio, and a racemic mixture thereof, and when two or more asymmetric carbon atoms exist in the compound, the compound may be in any form of an optically pure diastereomer, a racemic mixture thereof, and a combination thereof in an arbitrary ratio.

[0029]

The medical preparation including the compound of the present invention represented by the general formula (1) or pharmacologically acceptable salt thereof as an active ingredient may be administered orally or parenterally in a form of tablet, powder, granule, capsule, pill, suppository, injection,

eye-drops, solution, troche, aerosol, suspension, emulsion, syrup, or the like, mixed with a well-known pharmacologically acceptable carrier, excipient, diluent, extender, decaying agent, stabilizer, preservative, buffer, emulsifier, perfuming agent, colorant, sweetener, thickening agent, flavor, solubilizing agent, and other additives. Specific examples of the additives include: water; vegetable oil; alcohol such as ethanol or benzyl alcohol; carbohydrate such as glycol, glycerol triacetate, gelatin, lactose, or starch; magnesium stearate; potassium stearate; tarc; lanoline; vaseline; macrogol; crystalline cellulose; hydroxypropyl cellulose, and the like. While the dose may vary depending on the kind and degree of disease, the kind of the compound to be administered, the administration path, and the age, sex, and weight of the patient, in general, 0.1 to 5,000 mg, particularly 1 to 3,000 mg per one adult is preferably administered. In the case of a prodrug, it is preferable to administer 1 to 5,000 mg per adult.

[Effect of the Invention]

[0030]

The novel amine compound according to the present invention, a pharmacologically acceptable salt thereof, or a prodrug thereof can provide a novel CXCR4 antagonist. The novel CXCR4 antagonist of the present invention has a CXCR4 antagonism, and shows, based on the CXCR4 antagonism, excellent effects as a therapeutic or preventive drug for a disease such as: a viral infectious disease such as HIV; rheumatism; or cancer metastasis.

[Best Mode for carrying out the Invention]

[0031]

First, a method of producing a CXCR4 antagonist of the present invention will now be described in more detail with reference to production examples of the compound of the present invention. Hereinafter, unless particularly stated, reagents used are commercially available products (manufactured by e.g. Tokyo Kasei Kogyo Co. Ltd. (Tokyo), Kanto Chemical Co., Inc. (Tokyo), etc.) readily available to a person skilled in the art.

[Example 1]

[0032]

Production Example 1: Synthesis of 2-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-ethanol [Compound No. 1]

Example 1-1: Synthesis of 4-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-benzaldehyde

Methyl 4-(aminomethyl)-benzoate hydrochloride (manufactured by Aldrich Corporation) (773 mg) was dissolved in THF (50 ml) and then gradually added with lithium aluminum hydride (300 mg) under ice-cooling. The solution was stirred at room temperature for 3 hours and then cooled with ice, followed by gradual addition of a concentrated sodium hydroxide aqueous solution until foam was not observed. Filtration through Celite was carried out using chloroform as a solvent and then the filtrate was concentrated and dried. The dried product was dissolved in purified water (10 ml) and THF (10 ml). After having been cooled with ice, the solution was added with N-carbethoxyphthalimide

(1.26 g) and sodium carbonate (900 mg). After the mixture was stirred at room temperature for 4 hours, THF was distilled off and chloroform was then added to the residue to carry out extraction. The organic layer was dried with anhydrous sodium sulfate and the solvent was then distilled off. Subsequently, the residue was further dried under vacuum. Next, this compound was dissolved in chloroform (20 ml) and then added with manganese dioxide (chemically processed product) (5.0 g), followed by stirring at room temperature for 3 hours. After filtration through Celite, the filtrate was concentrated and then purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (259 mg) as a white solid.

MS(FAB,Pos.):m/z=266$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=4.92(2H,s),7.58(2H,d,J=8.3Hz),7.72-7.76(2H,m),7.83-7.89(4H,m),9.98(1H,s).

Example 1-2: Synthesis of N,N-dipropylbutane-1,4-diamine

N-(4-aminobutyl)-carbamic acid t-butyl ester (manufactured by Tokyo Kasei Kogyo Co., Ltd.) (500 mg) was dissolved in methanol (10 ml) and then added with propionaldehyde (manufactured by Tokyo Kasei Kogyo Co., Ltd.) (0.418 ml), sodium cyanoborohydride (404 mg), and trimethyl orthoacetate (1.60 g), and the whole was stirred at room temperature for 12 hours. After completion of the reaction, the solvent was distilled off. Then, the resultant was added with chloroform, washed with distilled water and a saturated saline solution, and then dried with anhydrous sodium sulfate. After concentration and evaporation to dryness of the solution, methanol (4.0 ml) and a 4 mol/l hydrogen chloride/dioxane solution (4.0 ml) were added to the dried product

and the whole was stirred at room temperature for 2 hours. After completion of the reaction, the solvent was distilled off and then dioxane was added to wash the residue, thereby obtaining a hydrochloride (654 mg) of the subject compound.

MS(FAB,Pos.):m/z=173[M+H]$^+$

Example 1-3: Synthesis of 2-{4-[(4-dipropylamino-butyl-amino)-methyl]-benzyl}-isoindol-1,3-dione

The compound (103 mg) obtained in Example 1-1 was dissolved in anhydrous methanol (10 ml) and then added with the hydrochloride (114 mg) of the compound obtained in Example 1-2. Then, the solution was added with triethylamine (0.108 ml) and anhydrous magnesium sulfate (3 g), followed by stirring at room temperature for 1 hour. Anhydrous magnesium sulfate was removed from the solution by filtration through Celite. Then, methanol was distilled off and the resultant was dried using a vacuum pump. The resultant was dissolved in anhydrous methanol (10 ml) and gradually added with sodium borohydride (22.0 mg) under ice-cooling. The solution was warmed back to room temperature and then stirred for 1 hour. After completion of the reaction, methanol was distilled off and the residue was then added with water and chloroform to extract the organic layer. After the organic layer was dried with anhydrous sodium sulfate, the solvent was distilled off and the residue was then purified through silica gel column chromatography (chloroform/methanol/water), thereby obtaining the subject compound (60.3 mg) as a pale-yellow viscous liquid.

MS(FAB,Pos.):m/z=420[M+H]$^+$

Example 1-4: Synthesis of [4-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-benzyl]-(4-dipropylamino-butyl)-carbamic acid t-butyl ester

The compound (60.3 mg) obtained in Example 1-3 was dissolved in chloroform and then added with di-t-butyldicarbonate (47.0 mg). After having been stirred at room temperature for 30 minutes, the solution was subjected to concentration and then purification through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (70.0 mg) as a colorless viscous liquid.

MS(FAB,Pos.):m/z=522 $[M+H]^+$

Example 1-5: Synthesis of (4-aminomethyl-benzyl)-(4-dipropylamino-butyl)-carbamic acid t-butyl ester

The compound (70.0 mg) obtained in Example 1-4 was added with a 40% methylamine/methanol solution (3.0 ml) and then stirred at room temperature for 14 hours. After completion of the reaction, the solvent was distilled off. Then, the residue was added with a 1 mol/l sodium hydroxide aqueous solution and chloroform to extract the aqueous layer therefrom with chloroform. The extract was dried with anhydrous sodium sulfate and the solvent was distilled off, thereby obtaining the subject compound (65.5 mg) as a colorless viscous liquid.

[0033]

Example 1-6: Synthesis of (4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-amino]

-methyl}-benzyl)-carbamic acid t-butyl ester

The compound (0.78 g) obtained in Example 1-5 was dissolved in methanol (20 ml) and added with 2-imidazole carboxaldehyde (214 mg) and the whole was stirred at room temperature for 17 hours. After the solvent was distilled off, the resultant was dried under vacuum, dissolved in methanol (15 ml), and then added with sodium borohydride (217.8 mg). The whole was stirred at room temperature for 45 minutes. The reaction solution was added with a saturated aqueous ammonium chloride solution (10 ml) and stirred at room temperature for 15 minutes.

Then, the reaction solution was added with a saturated saline solution and subjected to extraction with chloroform, followed by drying with anhydrous sodium sulfate. After the solvent was distilled off, the resultant residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (1.01 g) as a yellow solid.

MS(FAB,Pos.):m/z=472$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.3Hz),1.26-1.49(17H,m),2.32-2.35(6H,m),3.12(1H,brs),3.21(1H,brs),3.79(2H,brs),3.92(2H,brs),4.12(1H,brs),4.13(1H,brs),6.99(2H,s),7.20(2H,brs),7.25(2H,d,J=7.5Hz).

Example 1-7: Synthesis of (4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-carbamic acid t-butyl ester

The compound (231 mg) obtained in Example 1-6 was dissolved in anhydrous methanol (5.0 ml). The solution was added with sodium cyanoborohydride (61.6 mg), acetic acid (2.00 ml), and

1-methyl-2-imidazole carboxaldehyde (80.9 mg) and the whole was stirred at room temperature for 6 days under a nitrogen atmosphere. After completion of the reaction, the solvent was distilled off. The resultant was then dissolved in chloroform and added with a saturated aqueous sodium hydrogen carbonate solution and the whole was stirred for a while. The solution was subjected to extraction with chloroform and the extract was then washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. Subsequently, the solvent was distilled off and the residue was then purified through silica gel column chromatography (chloroform/methanol/water), thereby obtaining the subject compound (197 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=566$[M+H]^+$

Example 1-8: Synthesis of N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N',N'-dipropylbutane-1,4-diamine

The compound (197 mg) obtained in Example 1-7 was dissolved in methanol (1.0 ml) and added with a 10% hydrogen chloride/methanol solution (3.0 ml) and the whole was stirred overnight at room temperature. After completion of the reaction, the solvent was distilled off and a hydrochloride (159 mg) of the subject compound was obtained as a white solid.

MS(FAB,Pos.):m/z=466$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6+D_2O):δ=0.87(6H,t,J=7.3Hz),1.59-1.67(8H,m),2.87(2H,brs),2.94-2.97(4H,m),3.01(2H,brs),3.66(3H,s),3.69

(2H,s),4.03(4H,s),4.13(2H,s),7.34(2H,d,J=8.2Hz),7.39(2H,d,J=8.2Hz),7.40(1H,d,J=2.0Hz),7.41(1H,d,J=2.0Hz),7.53(2H,s).

Example 1-9: Synthesis of 2-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-ethanol [Compound No. 1]

The compound (209 mg) obtained in Example 1-8 was dissolved in anhydrous methanol (8.4 ml) and added with [1,4]-dioxan-2,5-diol (54.0 mg) and sodium cyanoborohydride (56.6 mg). Then, the solution was adjusted to pH 5 with acetic acid and stirred at room temperature for 19.5 hours. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution (1.0ml) and subjected to extraction with chloroform, followed by drying with magnesium sulfate. The solvent was distilled off and the residue was then purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (175.8 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=510$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6+D_2O):δ=0.92(6H,t,J=7.1Hz),1.64-1.68(6H,m),1.78-1.82(2H,m),3.00-3.08(10H,m),3.71(3H,s),3.74(4H,s),4.09(2H,s),4.17(2H,s),4.30(2H,q,J=13.9Hz),7.41(2H,d,J=7.8Hz),7.48(4H,d,J=5.6Hz),7.61(2H,s).

[Example 2]

[0034]

Production Example 2: Synthesis of

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 2]

Example 2-1: Synthesis of methyl 4-amino-3-{(5-t-butoxycarbonylamino)-pentanoyl}-aminobenzoate

In DMF (20 ml), 5-t-butoxycarbonylamino valeric acid (1.45 g), WSCI hydrochloride (1.74 g), and HOBt (1.25 g) were dissolved and the whole was stirred for 15 minutes. Then, the solution was added with methyl 3,4-diaminobenzoate (manufactured by Lancaster) (1.00 g) and the whole was stirred at room temperature for 4 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and then washed with a saturated aqueous ammonium chloride solution and a 1 mol/l sodium hydroxide aqueous solution. Subsequently, the resultant was subjected to extraction with chloroform and the extract was then washed with a saturated saline solution, followed by drying with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (1.46 g).

MS(FAB,Pos.):m/z=365$[M+H]^+$

Example 2-2: Synthesis of 2-(4-dipropylamino-butyl)-3H-benzimidazol-5-carboxylic acid methyl ester

The compound (1.46 g) obtained in Example 2-1 was dissolved in methanol (7.3 ml) and then added with a 4 mol/l hydrogen

chloride/dioxane solution (7.3 ml), followed by stirring overnight at 40°C. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was dried under vacuum. The dried product was dissolved in methanol (15 ml) and added with triethylamine (0.597 ml), trimethyl orthoformate (1.0 ml), and propionaldehyde (0.309 ml) and the whole was stirred at room temperature for 30 minutes. The solution was added with sodium cyanoborohydride (272 mg) and stirred at room temperature for 30 minutes. Furthermore, the solution was added with propionaldehyde (0.310 ml) and sodium cyanoborohydride (270 mg), followed by stirring at room temperature for 4 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and then washed with a 1 mol/l sodium hydroxide aqueous solution, followed by extraction with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure and the residue was then purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (315 mg) as a brown oily substance.

MS(FAB,Pos.):m/z=332$[M+H]^+$

Example 2-3: Synthesis of {4-[6-chloromethyl-1-(toluene-4-sulfonyl)-1H-benzimidazol-2-yl]-butyl}-dipropyl-amine

Lithium aluminum hydride (108 mg) was suspended in THF (60 ml) and a THF solution (60 ml) containing the compound (315 mg) obtained in Example 2-2 was dropped therein, and the whole was

stirred at room temperature for 1 hour. After completion of the reaction, sodium sulfate decahydrate was added to the solution until bubbling was stopped, and a 1 mol/l sodium hydroxide aqueous solution was then gradually added to the mixture until a white precipitate was generated. After filtration, the solvent was distilled off under reduced pressure. The residue was dried under vacuum, and the dried product was dissolved in dichloromethane (10 ml) and then added with triethylamine (263 μl) and p-toluenesulfonyl chloride (364 mg), followed by stirring at room temperature for 2.5 hours. After completion of the reaction, the solution was washed with water and subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure and the residue was then purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (113 mg) as a brown solid.

MS(FAB,Pos.):m/z=476$[M+H]^+$

Example 2-4: Synthesis of [4-(6-aminomethyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine

The compound (113 mg) obtained in Example 2-3 was dissolved in DMF (2.0 ml) and added with potassium phthalimide (69.0 mg), and the whole was stirred at room temperature for 2 days. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was then dissolved in chloroform, followed by washing with water. After extraction with chloroform, the organic layer was washed with a saturated saline solution

and dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was dried under vacuum, and the dried product was dissolved in a 40% methylamine/methanol solution (1.5 ml), followed by stirring overnight at room temperature. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was then dissolved in chloroform, followed by washing with water and a 1 mol/l sodium hydroxide aqueous solution. After extraction with chloroform, the extract was washed with a saturated saline solution and dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure and the residue was then purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (39.8 mg) as a brown solid.

MS(FAB,POS.):M/Z=303$[M+H]^+$

Example 2-5: Synthesis of [4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 2]

The compound (39.8 mg) obtained in Example 2-4 was dissolved in methanol (1.0 ml) and then added with 2-imidazole carboxaldehyde (13.3 mg) and trimethyl orthoformate (0.030 ml) and the whole was stirred at room temperature for 30 minutes. The solution was gradually added with sodium borohydride (10.5 mg), followed by stirring at room temperature for 1 hour. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was then dissolved in chloroform. After having been washed with water, the solution was subjected to

extraction with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure.

The resultant was dissolved in methanol (1.0 ml) and added with 1-methyl-2-imidazole carboxaldehyde (63.2 mg), acetic acid (0.023 ml), trimethyl orthoformate (0.030 ml), and sodium cyanoborohydride (23.2 mg) and the whole was stirred at room temperature for 30 minutes. The solution was added with acetic acid (0.045 ml) and stirred at room temperature for 4 hours. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was then dissolved in chloroform. After having been washed with a 1 mol/l sodium hydroxide aqueous solution, the solution was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (27.6 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=477$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.89(3H,t,J=7.3Hz),1.63-1.69(4H,m),1.70-1.81(2H,m),1.94-2.01(2H,m),2.84-3.00(4H,m),3.03-3.09(2H,m),3.19-3.23(2H,m),3.72(3H,s),3.90(2H,s),4.13(2H,s),4.21(2H,s),4.41(2H,t,J=7.3Hz),7.49(1H,s),7.53(1H,s),7.59(1H,d,J=8.4Hz),7.64-7.66(3H,m),7.81(1H,s),10.50(1H,s).

[Example 3]

[0035]

Production example 3: Synthesis of [4-(6-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 3]

Example 3-1: Synthesis of methyl 4-amino-3-propylamino-benzoate

In DMF (40 ml), methyl 3,4-diaminobenzoate (2.01 g) was dissolved and then the solution was added with potassium carbonate (2.00 g) and methyl iodide (1.4 ml) and the whole was stirred at room temperature for 22 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in ethyl acetate and washed with water, followed by extraction with ethyl acetate. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure and the residue was then purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (1.06 g).

MS(FAB,Pos.):m/z=209$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=1.05(3H,t,J=7.3Hz),1.71(2H,sext.,J=7.3Hz),3.12(2H,t,J=7.1Hz),3.86(3H,s),6.69(1H,d,J=8.1Hz),7.35(1H,s),7.45(1H,d,J=8.1Hz).

Example 3-2: Synthesis of methyl 4-(5-t-butoxycarbonylamino-pentanoylamino)-3-propylamino-benzoate

In chloroform (10 ml), 5-t-butoxycarbonylamino valeric acid (574 mg), WSCI hydrochloride (690 mg), and HOBt (487 mg) were dissolved. Then, the solution was stirred at room temperature for 30 minutes. The solution was added with the compound (503

mg) obtained in Example 3-1 and stirred overnight at room temperature. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was then dissolved in chloroform. After having been washed with a saturated aqueous sodium hydrogen carbonate solution, a saturated aqueous ammonium chloride solution, and a saturated saline solution, the resultant was dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure and the residue was then purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (540 mg) as a colorless viscous substance.

MS(FAB,Pos.):m/z=408$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.97(3H,t,J=7.3Hz),1.37(9H,s),1.37-1.46(2H,m),1.51-1.66(4H,m),2.37(2H,t,J=7.3Hz),2.93(2H,q,J=6.6Hz),3.04(2H,q,J=7.1Hz),3.81(3H,s),5.14(1H,br),6.83(1H,br),7.16(1H,s),7.20(1H,d,J=8.1Hz),7.45(1H,d,J=8.1Hz),9.24(1H,s).

Example 3-3: Synthesis of 2-(4-dipropylamino-butyl)-3-propyl-3H-benzimidazol-5-carboxylic acid methyl ester

The compound (540 mg) obtained in Example 3-2 was dissolved in methanol (10 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (5.0 ml) and the whole was stirred at room temperature for 1.5 hours. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was then dissolved in methanol, followed by neutralization with the addition of an anion-exchange resin (Amberlite IRA-410). The solvent was distilled off.

The resultant was then dissolved in methanol (12 ml). Subsequently, the solution was added with acetic acid (0.425 ml) and sodium cyanoborohydride (135 mg), followed by cooling to 0°C. The solution was added with propionaldehyde (0.114 ml) and stirred at room temperature for 1 hour, followed by cooling to 0°C again. The solution was added with sodium cyanoborohydride (132 mg) and propionaldehyde (0.115 ml) and then stirred overnight at room temperature. After completion of the reaction, the solvent was distilled off under reduced pressure and then the residue was dissolved in chloroform. The solution was washed with a 1 mol/l sodium hydroxide aqueous solution and then subjected to extraction with chloroform.

The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure and the residue was then purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (361 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=374$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.88(6H,t,J=7.3Hz),1.00(3H,t,J=7.3Hz),1.49(4H,q,J=7.5Hz),1.74-1.82(4H,m),1.87(2H,sext.,J=7.6Hz),1.91-2.09(4H,m),2.93-3.01(4H,m),3.00(2H,t,J=7.1Hz),3.09(2H,t,J=7.6Hz),3.96(3H,s),4.15(2H,t,J=7.6Hz),7.66(1H,d,J=8.5Hz),7.96(1H,d,J=8.5Hz),8.08(1H,s).

Example 3-4: Synthesis of [2-(4-dipropylamino-butyl)-3-propyl-3H-benzimidazol-5-yl]-methanol

Lithium aluminum hydride (138 mg) was suspended in THF (7.0

ml) and then the whole was cooled to 0°C. After that, a THF solution (7.0 ml) containing the compound (361 mg) obtained in Example 3-3 was dropped in the suspension, followed by stirring at 0°C for 1 hour. After completion of the reaction, sodium sulfate decahydrate was added to the solution until bubbling was stopped, and a 1 mol/l sodium hydroxide aqueous solution was then added to the mixture until a white precipitate was generated. The solid component was separated through filtration and the solvent was then distilled off from the filtrate under reduced pressure. The residue was dried under vacuum, thereby obtaining the subject compound (302 mg) as a pale-yellow oily substance.

MS(FAB,Pos.):m/z=346$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.82(6H,t,J=7.3Hz),0.89(3H,t,J=7.3Hz),1.37(4H,sext.,J=7.3Hz),1.50(2H,quint.,J=7.3Hz),1.70-1.81(4H,m),2.29(4H,t,J=7.3Hz),2.39(2H,t,J=7.1Hz),2.84(2H,t,J=7.6Hz),4.11(2H,t,J=7.3Hz),4.59(2H,d,J=5.2Hz),5.16(1H,t,J=5.5Hz),7.09(1H,d,J=8.2Hz),7.42(1H,s),7.45(1H,d,J=8.2Hz).

Example 3-5: Synthesis of 2-[2-(4-dipropylamino-butyl)-3-propyl-3H-benzimidazol-5-ylmethyl]-isoindol-1,3-dione

The compound (302 mg) obtained in Example 3-4 was dissolved in toluene (6.0 ml) and added with triphenylphosphine (275 mg) and phthalimide (193 mg) and the whole was cooled to 0°C. In this solution, a 40% diethyl azodicarboxylate/toluene solution (452 mg) was dropped and the whole was stirred overnight at room temperature. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and washed with water. Then, the resultant was

subjected to extraction with chloroform and washed with a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure and the residue was then purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (174 mg) as a pale-yellow solid.

MS(FAB,Pos.):m/z=475$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.79-0.83(6H,m),0.86(3H,t,J=7.3Hz),1.31-1.40(4H,m),1.46-1.51(2H,m),1.63-1.80(4H,m),2.29(4H,br),2.39(2H,br),2.83(2H,t,J=7.6Hz),4.12(2H,t,J=7.3Hz),4.87(2H,s),7.08(1H,d,J=8.3Hz),7.46-7.48(2H,m),7.83-7.89(2H,m),7.90-7.93(2H,m).

Example 3-6: Synthesis of [4-(6-aminomethyl-1-propyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine

The compound (173 mg) obtained in Example 3-5 was dissolved in a 40% methylamine/methanol solution (1.8 ml) and the whole was stirred at room temperature for 17 hours. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was then purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (130 mg) as a pale-yellow oily substance.

MS(FAB,Pos.):m/z=345$[M+H]^+$

Example 3-7: Synthesis of [4-(6-{[bis-(1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 3]

The compound (130 mg) obtained in Example 3-6 was dissolved in methanol (3.0 ml) and added with trimethyl orthoformate (0.130 ml) and 2-imidazole carboxaldehyde (37.3 mg) and the whole was stirred for 1 hour. After having been cooled to 0°C, the solution was added with sodium borohydride (21.5 mg) and stirred at room temperature for 3 hours. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was then dissolved in chloroform. The solution was washed with a 1 mol/l sodium hydroxide aqueous solution and then subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. Then, the residue was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (16.4 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=505$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.91(6H,t,J=7.3Hz),0.99(3H,t,J=7.3Hz),1.66-1.71(4H,m),1.78-1.82(4H,m),1.83-1.96(2H,m),2.97-3.00(4H,m),3.08-3.16(2H,m),3.25(2H,t,J=7.2Hz),3.87(2H,s),4.16(4H,s),4.54(2H,t,J=7.7Hz),7.52-7.55(1H,m),7.61(3H,s),7.64-7.70(1H,m),8.43(1H,s),10.31(1H,br).

[Example 4]

[0036]

Production example 4: Synthesis of [4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 4]

Example 4-1: Synthesis of [4-(6-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine

The compound (130 mg) obtained in Example 3-6 was dissolved in methanol (3.0 ml) and added with trimethyl orthoformate (0.130 ml) and 2-imidazole carboxaldehyde (37.3 mg) and the whole was stirred for 1 hour. After having been cooled to 0°C, the solution was added with sodium borohydride (21.5 mg) and stirred at room temperature for 3 hours. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was then dissolved in chloroform. The solution was washed with a 1 mol/l sodium hydroxide aqueous solution and then subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. Then, the residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (64.0 mg) as a pale-yellow oily substance.

[0037]

Example 4-2: Synthesis of [4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 4]

The compound (64.0 mg) obtained in Example 4-1 was dissolved in methanol (1.3 ml) and added with acetic acid (0.065 ml) and 1-methyl-2-imidazole carboxaldehyde (16.6 mg) and the whole was cooled to 0°C. Then, the solution was added with sodium

cyanoborohydride (14.2 mg) and stirred at room temperature for 2 days. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was then dissolved in chloroform. After washing with a 1 mol/l sodium hydroxide aqueous solution, the solution was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate.

After filtration, the solvent was distilled off under reduced pressure. Subsequently, the residue was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (30.0 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=519[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.91(6H,t,J=7.3Hz),0.99(3H,t,J=7.3Hz),1.66-1.74(4H,m),1.78-1.84(4H,m),1.93(2H,t,J=7.3Hz),2.94-3.00(4H,m),3.13(2H,br),3.26(2H,t,J=7.3Hz),3.73(3H,s),3.90(2H,s),4.13(2H,s),4.21(2H,s),4.53(2H,t,J=7.6Hz),7.53-7.55(3H,m),7.63(2H,s),7.70(1H,d,J=8.2Hz),8.41(1H,s),10.48(1H,br).

[Example 5]

[0038]

Production example 5: Synthesis of [4-(5-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 5]

Example 5-1: Synthesis of 3-nitro-4-propylamino-benzonitrile

In DMF (20 ml), 3-nitro-4-aminobenzonitrile (1.12 g) was dissolved, and the solution was added with 60% sodium hydride

(411 mg), followed by stirring at room temperature for 30 minutes. The solution was added with 1-iodopropane (805 μl) and stirred at room temperature for 1 hour. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was then dissolved in ethyl acetate. The resultant was washed with water and then subjected to extraction with ethyl acetate. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate.

After filtration, the solvent was distilled off under reduced pressure, thereby obtaining a crude product (1.58 g) of the subject compound as a yellow solid.

MS(FAB,Pos.):m/z=206$[M+H]^+$

Example 5-2: Synthesis of 3-amino-4-propylamino-benzonitrile

In ethanol (170 ml), the compound (1.58 g) obtained in Example 5-1 and stannous chloride dihydrate (7.81 g) were dissolved. Then, the solution was heated to 60°C and sodium borohydride (144 mg) was gradually added therein, followed by stirring at 60°C for 2 hours. After completion of the reaction, water was added to the solution, and the whole was neutralized with a 1 mol/l sodium hydroxide aqueous solution. Then, ethanol was distilled off under reduced pressure. The resultant was subjected to extraction with ethyl acetate. The extract was washed with a saturated saline solution and dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (1.18 mg) as a pale-yellow solid.

MS(FAB,Pos.):m/z=176$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=1.04(3H,t,J=7.6Hz),1.70(2H,sext.,J=7.3 Hz),3.13(2H,q,J=7.1Hz),6.58(1H,d,J=8.1Hz),6.94(1H,s),7.17(1H ,d,J=8.1Hz).

Example 5-3: Synthesis of t-butyl [4-(5-cyano-2-propylamino-phenylcarbamoyl)-butyl]-carbamate

In chloroform (31 ml), 5-t-butoxycarbonylamino valeric acid (1.57 g), WSCI hydrochloride (1.98 g), and HOBt (1.39 g) were dissolved. Then, the solution was stirred at room temperature for 30 minutes. The solution was dropped in a chloroform solution (10 ml) containing the compound (1.18 g) obtained in Example 5-2. Then, the whole was stirred at room temperature for 12 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and then washed with a saturated aqueous sodium hydrogen carbonate solution, a saturated aqueous ammonium chloride solution, and a saturated saline solution, followed by drying with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure and the residue was then purified through silica gel column chromatography (chloroform/ethyl acetate) to remove only highly-polar components, thereby obtaining a mixture (2.52 g) containing the subject compound as a yellow oily substance.

MS(FAB,Pos.):m/z=375$[M+H]^+$

Example 5-4: Synthesis of 2-(4-dipropylamino-butyl)-1-propyl-1H-benzimidazol-5-carbonitrile

The compound (2.52 g) obtained in Example 5-3 was dissolved

in methanol (20 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (12 ml) and the whole was stirred at room temperature for 2 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and washed with a 1 mol/l sodium hydroxide aqueous solution, followed by extraction with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure.

The resultant was dissolved in methanol (40 ml). Then, the solution was added with acetic acid (0.250 ml) and propionaldehyde (1.21 ml), followed by cooling to 0°C. The solution was added with sodium cyanoborohydride (1.39 g) and stirred at room temperature for 13 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and washed with a 1 mol/l sodium hydroxide aqueous solution, followed by extraction with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure and the residue was then purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (1.41 g) as a yellow oily substance.
MS(FAB,Pos.):m/z=341$[M+H]^+$

Example 5-5: Synthesis of
[4-(5-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 5]

Lithium aluminum hydride (588 mg) was suspended in THF (30 ml) and then the whole was cooled to 0°C. After that, a THF solution (30 ml) containing the compound (1.40 g) obtained in Example 5-4 was dropped in the suspension and the whole was stirred at 0°C for 1 hour. After completion of the reaction, sodium sulfate decahydrate was added to the solution until bubbling was stopped, and a 1 mol/l sodium hydroxide aqueous solution was then added to the mixture until a white precipitate was generated. A solid component was separated through filtration and the solvent was then distilled off from the filtrate under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol).

The purified product was dissolved in methanol (12 ml) and added with trimethyl orthoformate (0.78 ml) and 2-imidazole carboxaldehyde (228 mg), followed by stirring for 1 hour. Then, the solution was cooled to 0°C. The solution was added with sodium borohydride (188 mg) and stirred at room temperature for 1 hour. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was then dissolved in a 1 mol/l hydrochloric acid. The aqueous layer was washed with chloroform. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. Then, the residue was purified through silica gel column chromatography (chloroform/ethyl acetate).

The purified product was dissolved in methanol (6.0 ml) and then added with acetic acid (0.20 ml) and sodium

cyanoborohydride (50.0 mg). The solution was gradually added with 1-methyl-2-imidazole carboxaldehyde (59.8 mg), followed by stirring at room temperature for 6 hours. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was then dissolved in chloroform. After having been washed with a 1 mol/l sodium hydroxide aqueous solution, the solution was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (242 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=519$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.89-0.95(9H,m),1.67-1.94(10H,m),2.96-3.00(4H,m),3.12-3.13(2H,m),3.26(2H,t,J=7.3Hz),3.72(3H,s),3.91(2H,s),4.13(2H,s),4.21(2H,s),4.41(2H,t,J=7.3Hz),7.49(1H,s),7.52(1H,s),7.64(2H,s),7.72(1H,d,J=8.5Hz),7.82(1H,s),7.90(1H,d,J=8.5Hz),10.61(1H,s).

[Example 6]

[0039]

Production example 6: Synthesis of 4-{[N-(1H-imidazol-2-ylmethyl)-amino]-methyl-N-(4-dipropylamino-butyl)-benzamide [Compound No. 6]

Example 6-1: Synthesis of 4-{[t-butoxycarbonyl-(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzoic acid

Commercially available methyl bromomethylbenzoate (manufactured by Aldrich Corporation) (10.0 g) was dissolved in DMF (100 ml), and the solution was added with potassium phthalimide (manufactured by Tokyo Kasei Kogyo Co., Ltd.) (9.70 g) and the whole was stirred at room temperature for 1.5 hours. After completion of the reaction, the solution was concentrated and added with water, followed by extraction with chloroform. The resultant was washed with a saturated saline solution and dried with anhydrous sodium sulfate, and the solvent was distilled off, thereby obtaining a white solid (12.9 g). Subsequently, 7.56 g of the solid was dissolved in methanol (100 ml), and the solution was added with hydrazine monohydrate (manufactured by Nacalai Tesque, Inc.) (6.25 ml) and the whole was stirred at 60°C for 1.5 hours. After completion of the reaction, the precipitated solid was filtrated out and the solvent was distilled off. The resultant was added with water and subjected to extraction with chloroform. The resultant was washed with a 0.3 mol/l sodium hydroxide aqueous solution and a saturated saline solution and dried with anhydrous sodium sulfate, and the solvent was distilled off. Methanol (120 ml) and 2-imidazole carboxaldehyde (manufactured by Aldrich Corporation) (2.35 g) were added to the resultant and the whole was stirred at room temperature for 2 days. After completion of the reaction, the precipitated solid was filtrated out. The liquid layer was concentrated and evaporated to dryness, and washing was performed by adding anhydrous methanol (30 ml). Then, the solid was filtrated out. The resultant solid and the solid that had been previously filtrated out were suspended in methanol (86 ml), and sodium borohydride (1.42 g) was added under ice-cooling. The solution

was stirred at room temperature for 1 hour, and the solvent was distilled off. After addition of water, extraction was performed with chloroform, and the organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate, followed by concentration under reduced pressure and drying, thereby obtaining a colorless oily substance (4.32 g). 4.28 g of the oily substance was dissolved in DMF (65 ml), and the solution was added with di-t-butyldicarbonate (8.90 ml) and stirred at room temperature for 1 hour.

After completion of the reaction, the solvent was distilled off, and the residue was dissolved in chloroform, followed by washing with a saturated saline solution. After drying with anhydrous sodium sulfate, the solvent was distilled off, and THF (43 ml), methanol (43 ml), and a 1 mol/l sodium hydroxide aqueous solution (43 ml) were added to the resultant, followed by stirring at room temperature for 14 hours. After completion of the reaction, the solvent was distilled off, and water (5.0 ml) was added to the resultant. Further, 1 mol/l hydrochloric acid was carefully added to the solution, and the acid-precipitate was filtrated out and dried, thereby obtaining the subject compound (4.87 g) as a white solid.

MS(FAB,Pos.):m/z=332$[M+H]^+$

Example 6-2: Synthesis of [4-(4-dipropylamino-butylcarbamoyl)-benzyl]-(1H-imidazol-2-ylmethyl)-carbamic acid t-butyl ester

The compound (203 mg) obtained in Example 1-2 was dissolved in DMF (5.0 ml) and chloroform (5.0 ml), and then added with triethylamine (0.374 ml), WSCI hydrochloride (382 mg), HOBt (200

mg), and the compound (463 mg) obtained in Example 6-1. The whole was stirred at room temperature for 23 hours. After completion of the reaction, the solvent was distilled off. Then, the resultant was added with chloroform and washed with water and a saturated saline solution, followed by drying with anhydrous sodium sulfate. The solvent was distilled off and the residue was purified through silica gel column chromatography (chloroform/methanol/water), thereby obtaining the subject compound (168 mg) as colorless foam.

MS(FAB,Pos.):m/z=486$[M+H]^+$

Example 6-3: Synthesis of 4-{[N-(1H-imidazol-2-ylmethyl)-amino]-methyl-N-(4-dipropylamino-butyl)-benzamide [Compound No. 6]

The compound (117 mg) obtained in Example 6-2 was dissolved in methanol (1.2 ml) and then added with a 4 mol/l hydrogen chloride/dioxane solution (1.2 ml) and the whole was stirred at room temperature for 5 hours. After completion of the reaction, the solvent was distilled off. Then, the residue was dissolved in water and then purified through solid-phase extraction column (Sep-Pak, tC18, manufactured by Waters Corporation), thereby obtaining a hydrochloride (118 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=386$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.89(6H,t,J=7.3Hz),1.54-1.62(2H,m),1.61-1.83(6H,m),2.93-3.01(4H,m),3.00-3.01(2H,m),3.30(2H,dd,J=6.1,12.3Hz),4.37(2H,s),4.52(2H,s),7.62-7.64(4H,m),7.92(2H,d,J=8.1Hz),8.71(1H,d,J=4.4Hz).

[Example 7]

[0040]

Production example 7: Synthesis of 2-(4-dipropylamino-butyl)-5-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-2,3-dihydro-isoindol-1-one [Compound No. 7]

Example 7-1: Synthesis of 4-methyl phthalic acid dimethyl ester

In methanol (60 ml), 4-methylphthalic acid (3.00 g) was dissolved. Then, WSCI hydrochloride (9.62 g) and 4-dimethylaminopyridine (3.07 g) were added to the solution, and the whole was stirred at room temperature for 3.5 hours. The reaction solution was added with water to stop the reaction and then the whole was subjected to extraction with chloroform. The organic layer was washed with water, 1 mol/l hydrochloric acid, and a saturated saline solution, and then dried with anhydrous sodium sulfate. The solvent was distilled off and the residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (2.54 g) as a colorless oily substance.

MS(FAB,Pos.):m/z=209$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=2.42(3H,s),3.89(3H,s),3.91(3H,s),7.33(1H,dd,J=1.7,8.6Hz),7.47(1H,d,J=1.2Hz),7.68(1H,d,J=7.8Hz).

Example 7-2: Synthesis of 4-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-phthalic acid dimethyl ester

The compound (202 mg) obtained in Example 7-1 was dissolved in carbon tetrachloride (7.1 ml) and added with N-bromosuccinimide (205 mg) and 2,2'-azobisisobutyronitrile (15.8 mg) and the whole

was refluxed under heating for 20 hours. The solution was further added with carbon tetrachloride (7.0 ml) and N-bromosuccinimide (51.3 mg) and the whole was refluxed under heating for additional 4 hours. After having been left for cooling, the solution was added with water to stop the reaction and then subjected to extraction with chloroform. The organic layer was washed with water and a saturated saline solution and then dried with anhydrous sodium sulfate. The solvent was distilled off and the residue was then dissolved in DMF (5.8 ml). The solution was added with potassium phthalimide (359 mg) and stirred at room temperature for 16 hours. The residue obtained by distilling the solvent off was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (226 mg) as a white solid.

MS(FAB,Pos.):m/z=354$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=3.88(3H,s),3.90(3H,s),4.89(2H,s),7.60(1H,dd,J=1.8,8.1Hz),7.71(1H,d,J=7.9Hz),7.74(2H,dd,J=2.9,5.5Hz),7.75(1H,m),7.87(2H,dd,J=2.9,5.5Hz).

Example 7-3: Synthesis of
4-(t-butoxycarbonylamino-methyl)-phthalic acid dimethyl ester

The compound (909 mg) obtained in Example 7-2 was suspended in methanol (22 ml). Hydrazine monohydrate (0.13 ml) was dropped in this suspension and the whole was refluxed under heating for 4 hours. After completion of the reaction, the solvent was distilled off under reduced pressure and then the residue was subjected to extraction with chloroform. The organic layer was washed with water and then with a saturated saline solution, followed by drying with anhydrous sodium sulfate. The residue

obtained by distilling the solvent off was dissolved in DMF (15 ml) and added with triethylamine (0.54 ml) and di-t-butyldicarbonate (851 mg), followed by stirring at room temperature for 15 hours. After the solvent was distilled off, the residue was subjected to extraction with chloroform. The organic layer was washed with water and a saturated saline solution and then dried with anhydrous sodium sulfate. The residue obtained by distilling the solvent off was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (779 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=324$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=1.47(9H,s),3.90(3H,s),3.91(3H,s),4.38(2H,d,J=6.1Hz),4.94(1H,br),7.46(1H,d,J=8.5Hz),7.61(1H,d,J=1.5Hz),7.72(1H,d,J=7.8Hz).

Example 7-4: Synthesis of 4-(t-butoxycarbonylamino-methyl)-phthalic acid

The compound (76.4 mg) obtained in Example 7-3 was dissolved in methanol (4.5 ml). A 1 mol/l sodium hydroxide aqueous solution (2.3 ml) was dropped in this solution and the whole was stirred at room temperature for 2 hours. The solution was neutralized by addition of 1 mol/l hydrochloric acid (2.3 ml). The residue obtained by distilling the solvent off was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (65.3 mg) as a pale-yellow oily substance.

MS(FAB,Pos.):m/z=296$[M+H]^+$

^{1}H-NMR(500MHz,CD_3OD):δ=1.45(9H,s),4.30(2H,s),7.45(1H,d,J=7.6Hz),7.80(1H,s),7.88(1H,d,J=8.1Hz).

Example 7-5: Synthesis of
[2-(4-di-n-propylamino-butyl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-ylmethyl]-carbamic acid t-butyl ester

The compound (123 mg) obtained in Example 7-4 was dissolved in xylene (5.0 ml). A xylene solution (5.0 ml) containing the compound (83.4 mg) obtained in Example 1-2 was dropped to the solution and the whole was refluxed under heating for 63 hours. The solution was added with water to stop the reaction and then subjected to extraction with chloroform. The organic layer was washed with water and a saturated saline solution, followed by drying with anhydrous sodium sulfate. The residue obtained by distilling the solvent off was then purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (88.4 mg) as a yellow solid.

MS(FAB,Pos.):m/z=432$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.85(6H,t,J=7.4Hz),1.40-1.50(6H,m),1.47(9H,m),1.64-1.70(2H,m),2.34(4H,t,J=7.4Hz),2.42(2H,t,J=7.5Hz),3.69(2H,t,J=7.3Hz),4.45(2H,d,J=6.1Hz),5.04(1H,br),7.62(,1H.d,J=7.5Hz),7.76(1H,d,J=0.8Hz),7.79(1H,d,J=7.6Hz).

Example 7-6: Synthesis of
N-[2-(4-dipropylamino-butyl)-1-oxo-2,3-dihydro-1H-isoindol-5-ylmethyl]-acetamide and
N-[2-(4-dipropylamino-butyl)-3-oxo-2,3-dihydro-1H-isoindol-5-ylmethyl]-acetamide

The compound (86.5 mg) obtained in Example 7-5 was dissolved in acetic acid (2.0 ml) and the whole was heated to 60°C. The solution was added with a zinc powder (130 mg) in several additions,

followed by refluxing under heating for 10 hours. After cooling the solution to room temperature, the solution was subjected to filtration through Celite and concentrated. The resultant was neutralized with a saturated aqueous sodium hydrogen carbonate solution and subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution, and then dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining a mixture (66.1 mg) of the subject compounds as a yellow oily substance.

1-oxo compound

MS(FAB,Pos.):m/z=360$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.85(6H,t,J=7.3Hz),1.39-1.48(6H,m),1.65-1.68(2H,m),2.07(3H,s),2.32(4H,m),2.43(2H,t,J=7.3Hz),3.61(2H,t,J=7.3Hz),4.34(2H,s),4.52(2H,d,J=5.8Hz),6.14(1H,br),7.33(1H,d,J=7.8Hz),7.38(1H,s),7.74(1H,d,J=7.8Hz).

3-oxo compound

MS(FAB,Pos.):m/z=360$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.85(6H,t,J=7.3Hz),1.39-1.48(6H,m),1.65-1.68(2H,m),2.05(3H,s),2.32(4H,m),2.43(2H,t,J=7.3Hz),3.62(2H,t,J=7.3Hz),4.35(2H,s),4.51(2H,d,J=5.8Hz),6.14(1H,br),7.40(1H,s),7.47(1H,dd,J=1.6,7.7Hz),7.70(1H,d,J=1.0Hz).

Example 7-7: Synthesis of 2-(4-dipropylamino-butyl)-5-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-2,3-dihydro-isoindol-1-one

The compound (66.1 mg) obtained in Example 7-6 was added with 1 mol/l hydrochloric acid, followed by refluxing under heating for 18 hours. The residue obtained by concentration was dissolved

in methanol and added with an anion-exchange resin (Amberlite IRA-410) to adjust the solution to pH 8. The resin was filtrated out and the solvent in the filtrate was distilled off. Subsequently, the residue was dissolved in methanol (2.0 ml) and added with trimethyl orthoformate (0.070 ml) and 2-imidazole carboxaldehyde (28.8 mg), followed by stirring at room temperature for 20 hours. After having been cooled to 0°C, the solution was added with sodium borohydride (22.7 mg) and stirred for 3 hours after having been warmed to room temperature. Then, the solution was added with water to stop the reaction and subjected to extraction with chloroform.

The organic layer was washed with water and a saturated saline solution and dried with anhydrous sodium sulfate. The residue obtained by distilling the solvent off was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (13.4 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=398$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.85(6H,t,J=7.3Hz),1.39-1.52(6H,m),1.64-1.70(2H,m),2.34-2.36(4H,m),2.44(2H,t,J=7.3Hz),3.62(2H,t,J=7.2Hz),3.89(2H,s),3.94(2H,s),4.34(2H,s),7.00(2H,s),7.39(1H,d,J=6.7Hz),7.40(1H,s),7.76(1H,d,J=8.1Hz).

Example 7-8: Synthesis of 2-(4-dipropylamino-butyl)-5-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-2,3-dihydro-isoindol-1-one [Compound No. 7]

The compound (20.3 mg) obtained in Example 7-7 was dissolved in methanol (2.0 ml). The solution was added with

1-methyl-2-imidazole carboxaldehyde (6.8 mg) and sodium cyanoborohydride (6.4 mg). The solution was adjusted to pH 4 by addition of acetic acid, followed by stirring at room temperature for 6 hours. Then, the solution was added with a saturated aqueous sodium hydrogen carbonate solution to stop the reaction and then subjected to extraction with chloroform. After that, the organic layer was washed with water and a saturated saline solution and then dried with anhydrous sodium sulfate. After the solvent was distilled off, the residue was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (24.0 mg) of the subject compound as a pale-yellow solid.

MS(FAB,Pos.):m/z=492$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.85(6H,t,J=7.4Hz),1.39-1.52(6H,m),1.65(2H,m),2.33-2.36(4H,m),2.44(2H,t,J=7.4Hz),3.51(2H,s),3.59(3H,s),3.60(2H,s),3.63(2H,t,J=7.5Hz),3.77(2H,s),4.37(2H,s),6.90(1H,d,J=1.5Hz),7.01(1H,d,J=1.2Hz),7.09(1H,br),7.12(1H,br),7.48(1H,s),7.57(1H,d,J=8.8Hz),7.82(1H,d,J=7.8Hz).

[Example 8]

[0041]

Production example 8: Synthesis of 2-(4-dipropylamino-butyl)-6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-2,3-dihydro-isoindol-1-one [Compound No. 8]

Example 8-1: Synthesis of 2-(4-dipropylamino-butyl)-6-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-2,3-dihydro-isoindol-1-one

The compound (66.1 mg) obtained in Example 7-6 was added with 1 mol/l hydrochloric acid, followed by refluxing under heating for 18 hours. The residue obtained by concentration was dissolved in methanol and added with an anion-exchange resin (Amberlite IRA-410) to adjust the solution to pH 8. The resin was filtrated out and the solvent in the filtrate was distilled off. The residue was dissolved in methanol (2.0 ml) and added with trimethyl orthoformate (0.070 ml) and 2-imidazole carboxaldehyde (28.8 mg), followed by stirring at room temperature for 20 hours. After having been cooled to 0°C, the solution was added with sodium borohydride (22.7 mg) and stirred for 3 hours after having been warmed to room temperature. Then, the solution was added with water to stop the reaction and subjected to extraction with chloroform.

The organic layer was washed with water and a saturated saline solution and dried with anhydrous sodium sulfate. The residue obtained by distilling the solvent off was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (22.9 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=398$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.85(6H,t,J=7.3Hz),1.39-1.52(6H,m),1.65-1.71(2H,m),2.33-2.36(4H,m),2.44(2H,t,J=7.3Hz),3.64(2H,t,J=7.3Hz),3.89(2H,s),3.93(2H,s),4.37(2H,s),7.00(2H,s),7.39(1H,d,J=7.8Hz),7.46(1H,d,J=7.8Hz),7.86(1H,s).

Example 8-2: Synthesis of 2-(4-dipropylamino-butyl)-6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-2,3-dihydro-isoi

ndol-1-one [Compound No. 8]

The compound (15.1 mg) obtained in Example 8-1 was dissolved in methanol (1.5 ml). The solution was added with 1-methyl-2-imidazole carboxaldehyde (5.0 mg) and sodium cyanoborohydride (4.8 mg). The solution was adjusted to pH 4 by addition of acetic acid, followed by stirring at room temperature for 2.5 hours. Then, the solution was added with a saturated aqueous sodium hydrogen carbonate solution to stop the reaction and then subjected to extraction with chloroform. After that, the organic layer was washed with water and a saturated saline solution and then dried with anhydrous sodium sulfate. After the solvent was distilled off, the residue was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (16.5 mg) of the subject compound as a pale-yellow solid.

MS(FAB,Pos.):m/z=492$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.85(6H,t,J=7.4Hz),1.39-1.52(6H,m),1.65-1.71(2H,m),2.33-2.36(4H,m),2.44(2H,t,J=7.3Hz),3.54(2H,s),3.57(2H,s),3.59-3.63(2H,m),3.61(3H,s),3.76(2H,s),4.37(2H,s),6.88(1H,s),6.89(1H,s),7.01(1H,s),7.02(1H,s),7.41(1H,dd,J=0.6,7.7Hz),7.59(1H,dd,J=1.6,7.7Hz),7.94(1H,d,J=0.8Hz).

[Example 9]

[0042]

Production example 9: Synthesis of N-(4-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N-methyl-N',N'-dipropyl-butane-1,4-diamine [Compound No. 9]

Example 9-1: Synthesis of

4-{[(4-dipropylamino-butyl)-methyl-amino]-methyl}-benzonitrile

The compound (185 mg) obtained in Example 1-2 was dissolved in anhydrous methanol (3.7 ml). The solution was added with 4-formyl benzonitrile (154 mg) and trimethyl orthoformate (0.351 ml) and the whole was stirred at room temperature. After completion of the reaction, the solvent was distilled off. Then, the resultant was added with water and subjected to extraction with chloroform. The extract was dried with magnesium sulfate and the solvent was distilled off under reduced pressure.

The resultant was dissolved in anhydrous methanol (9.2 ml) and added with a 36% formaldehyde aqueous solution (0.134 ml). The solution was added with sodium cyanoborohydride (201 mg) and adjusted to pH 5 by addition of acetic acid, followed by stirring at room temperature for 24 hours. The solution was added with a 1 mol/l sodium hydroxide aqueous solution and subjected to extraction with chloroform. The extract was dried with magnesium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (296 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=302$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.87(6H,t,J=7.3Hz),1.40-1.51(8H,m),2.17(3H,s),2.33-2.40(8H,m),3.51(2H,s),7.44(2H,dd,J=0.5,6.6Hz),7.60(2H,dd,J=2.0,6.6Hz).

Example 9-2: Synthesis of N-(4-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N-methyl-N',N'-dipropyl-butane-1,4-diamine [Compound No. 9]

The compound (13.2 g) obtained in Example 9-1 was dissolved in ethanol (530 ml) and a 1 mol/l sodium hydroxide aqueous solution (133 ml) and Raney nickel (1.3 g) were added thereto. The whole was stirred at room temperature for 4 hours under a hydrogen atmosphere.

After completion of the reaction, the resultant was subjected to filtration through Celite and the solvent was distilled off. The resultant was subjected to extraction with chloroform and dried with magnesium sulfate and the solvent was distilled off.

The resultant was dissolved in anhydrous methanol (580 ml) and added with 2-imidazole carboxaldehyde (5.07 g) and trimethyl orthoformate (14.4 ml), followed by stirring at room temperature for 3 hours. The solution was added with sodium borohydride (3.32 g) under ice-cooling, followed by stirring at room temperature for 2 hours. The solution was added with water and the solvent was distilled off, followed by extraction with chloroform. The extract was dried with magnesium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (13.0 g) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=386$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.90(6H,t,J=7.3Hz),1.63-1.81(8H,m),2.63(3H,d,J=4.6Hz),2.94-3.06(8H,m),4.36(2H,s),4.53(2H,s),7.67-7.71(6H,m),10.39(1H,brs),11.13(1H,brs).

[Example 10]

[0043]

Production example 10: Synthesis of N-methyl-N-[4-({[1-(1-methyl-1H-imidazol-2-ylmethyl)-1H-imidazol-2-ylmethyl]-amino}-methyl)-benzyl-N',N'-dipropylbutane-1,4-diamine [Compound No. 10]

Example 10-1: Synthesis of 2-hydroxymethyl-1-methyl imidazole

1-Methyl imidazole (42.1 g) and paraformaldehyde (5.00 g) were stirred under heating at 120°C for 3 hours.

Paraformaldehyde (13.0 g) was further added thereto and the whole was stirred at 120°C for 8 hours. The resultant was stirred at 120°C for additional 3 hours. The resultant was added with isobutyl acetate (40 ml) and the whole was refluxed at 135°C for 3 hours. The resultant was added with isobutyl acetate (40 ml) and stirred and left for cooling. The resultant was cooled to room temperature and subjected to filtration and washing with ethyl acetate, followed by drying, thereby obtaining the subject compound (36.2 g) as a white solid.

[0044]

Example 10-2: Synthesis of 2-chloromethyl-1-methyl imidazole hydrochloride

The compound (56.1 g) obtained in Example 10-1 was gradually added to thionyl chloride (119 ml) under ice-cooling. After completion of dropping, the whole was refluxed at 65°C for 15 minutes. Excess thionyl chloride was distilled off under reduced pressure and the solution was further subjected to azeotropic distillation with toluene, thereby obtaining a hydrochloride (82.4 g) of the subject compound as a yellow solid.

[0045]

Example 10-3: Synthesis of N-methyl-N-[4-({[1-(1-methyl-1H-imidazol-2-ylmethyl)-1H-imidazol-2-ylmethyl]amino}-methyl)-benzyl-N',N'-dipropylbutane-1,4-diamine [Compound No. 10]

The compound (39.1 mg) obtained in Example 9-2 was dissolved in DMF (0.80 ml) and added with 60% sodium hydride (12.2 mg) under a nitrogen atmosphere while the whole was stirred under ice-cooling. The solution was warmed back to room temperature. After having been stirred for 30 minutes, the resultant was added with the compound (16.9 mg) obtained in Example 10-2, followed by stirring at room temperature for 3 hours. The solution was added with water (18 μl) under ice-cooling to stop the reaction. After the solvent was distilled off under reduced pressure, the residue was dissolved in chloroform and added with water. The aqueous layer was extracted with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The reside was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (44.0 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=480$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.4Hz),1.40-1.52(8H,m),2.15(3H,s),2.34(4H,t,J=2.2Hz),2.37(2H,t,J=5.8Hz),2.39(2H,t,J=16.5Hz),3.45(2H,s),3.47(3H,s),3.81(2H,s),3.94(2H,s),6.75(1H,d,J=1.2Hz),6.86(1H,d,J=1.2Hz),6.93(1H,d,J=1.2Hz),7.01(1H,d,J=1.5Hz),7.26(2H,s),7.27(2H,s).

[Example 11]

[0046]

Production example 11: Synthesis of [4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1H-inden-2-yl)-butyl]-dipropyl-amine [Compound No. 11]

Example 11-1: Synthesis of 4-(t-butyldiphenylsilyloxy)-butane-1-ol

In DMF (120 ml), 1,4-butanediol (4.0 g) was dissolved. The solution was added with imidazole (3.02 g) and t-butyldiphenylchloro silane (12.2 g), and the whole was stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure and then added with a saturated aqueous ammonium chloride solution, followed by extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (6.56 g) as a colorless oily substance.

^{1}H-NMR(500MHz,$CDCl_3$):δ=1.05(9H,s),1.63-1.71(4H,m),2.05(1H,t,J=5.1Hz),3.66(2H,dt,J=5.1,5.9Hz),3.70(2H,t,J=5.9Hz),7.37-7.45(6H,m),7.67(4H,d,J=8.5Hz).

Example 11-2: Synthesis of 4-(t-butyldiphenylsilyloxy)butylaldehyde

The compound (6.56 g) obtained in Example 11-1 was dissolved in dichloromethane (262 ml) and then added with Molecular Sieves 4A (32.8 g), N-methylmorpholin-N-oxide (7.02 g), and tetrapropylammonium perruthenate (702 mg) and the whole was

stirred at room temperature for 2 hours. The reaction solution was filtrated through Celite and the filtrate was then concentrated under reduced pressure. The residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (3.86 g) as a colorless oily substance.

[0047]

Example 11-3: Synthesis of

5-bromo-2-[4-(t-butyldiphenylsilyloxy)butyliden]indan-1-one

In THF (75 ml), 5-bromoindanone (2.50 g) was dissolved. The solution was added with a 1 mol/l lithium bistrimethylsilyl amide/hexane solution (11.8 ml) while being stirred at -78°C, followed by stirring for 30 minutes. Subsequently, a THF solution (15 ml) containing the compound (3.86 g) obtained in Example 11-2 was gradually added to the solution, and the whole was stirred for additional 3 hours. The reaction solution was added with a saturated aqueous ammonium chloride solution and then subjected to extraction with chloroform. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was again dissolved in DMF (75 ml) and then the whole was added with methanesulfonyl chloride (2.71 g) and triethylamine (2.63 g) while being stirred under ice-cooling, followed by heating to room temperature and stirring for 1 hour. Subsequently, the solution was added with 1,8-diaza-bicyclo[5,4,0]undec-7-ene (3.97 g) and stirred at 70°C for 1 hour. The reaction solution was concentrated under reduced pressure and the residue was then added with a saturated aqueous ammonium chloride solution, followed by extraction with chloroform. The organic layer was

dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (hexane/diethyl ether), thereby obtaining the subject compound (4.56 g) as a brown oily substance.
^{1}H-NMR(500MHz,$CDCl_3$):δ=1.06(9H,s),1.77(2H,quint.,J=6.1Hz),2.42(2H,dt,J=6.1,7.6Hz),3.62(2H,s),3.71(2H,t,J=7.1Hz),6.88(1H,t,J=7.6Hz),7.34-7.44(7H,m),7.54(1H,d,J=8.3Hz),7.64(4H,d,J=8.1Hz),7.71(1H,d,J=8.3Hz).

Example 11-4: Synthesis of
5-bromo-2-[4-(t-butyldiphenylsilyloxy)butyl]indan-1-one

The compound (4.56 g) obtained in Example 11-3 was dissolved in THF (136 ml). Then, the solution was added with a 1 mol/l K-Selectride/THF solution (8.76 ml) while being stirred at-78°C, followed by stirring at the same temperature for 1 hour. The reaction solution was added with a saturated aqueous ammonium chloride solution and then subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified through silica gel column chromatography (hexane/diethyl ether), thereby obtaining the subject compound (2.03 g) as a yellow oily substance.

[0048]
Example 11-5: Synthesis of
5-bromo-2-[4-(t-butyldiphenylsilyloxy)butyl]indan-1-ol

The compound (2.03 g) obtained in Example 11-4 was dissolved in methanol (61 ml) and THF (31 ml) and added with sodium borohydride (0.442 g) under ice-cooling and the whole was stirred at room

temperature for 2 hours. The reaction solution was added with a saturated aqueous ammonium chloride solution and then subjected to extraction with chloroform. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (1.54 g) as a yellow oily substance.

[0049]

Example 11-6: Synthesis of [4-(5-bromo-1-methoxymethoxy-1-indan-2-yl)-butoxy]-t-butyldiphenylsilane

The compound (1.54 g) obtained in Example 11-5 was dissolved in DMF (46.2 ml) and added with 60% sodium hydride (235 mg) and chloromethylmethylether (592 mg) while the whole was stirred under ice-cooling, followed by stirring at room temperature for 24 hours. The reaction solution was added with water and subjected to extraction with chloroform. After having been washed with a saturated saline solution, the organic layer was dried with anhydrous sodium sulfate, concentrated under reduced pressure, and dried under vacuum. The residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (1.64 g) as a yellow oily substance.

[0050]

Example 11-7: Synthesis of 3-(5-bromo-1-methoxymethoxy-indan-2-yl)butylaldehyde

The compound (1.64 g) obtained in Example 11-6 was dissolved in THF (49.2 ml) and added with a 1 mol/l tetrabutyl ammonium

fluoride/THF solution (4.69 ml) and the whole was stirred at room temperature for 3 hours. The reaction solution was concentrated under reduced pressure and added with water, followed by extraction with chloroform. After having been washed with a saturated saline solution, the organic layer was dried with anhydrous sodium sulfate, concentrated under reduced pressure, and dried under vacuum. The residue was dissolved in dichloromethane (41 ml) again. Then, the solution was added with Molecular Sieves 4A (5.15 g), N-methylmorpholin-N-oxide (1.10 g), and tetrapropylammonium perruthenate (109 mg), followed by stirring at room temperature for 1 hour. The reaction solution was filtrated through Celite and the filtrate was then concentrated under reduced pressure. The residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (0.574 g) as a pale-yellow oily substance.

[0051]

Example 11-8: Synthesis of
5-bromo-2-(3-dipropylaminobutyl)-1-methoxymethoxy-indane

The compound (574.0 mg) obtained in Example 11-7 was dissolved in 1,2-dichloroethane (28.7 ml), added with di-n-propylamine (266.3 mg) and sodium triacetoxyborohydride (743.6 mg) while the whole was stirred at room temperature, followed by stirring for 20 hours. The reaction solution was added with a 1 mol/l sodium hydroxide aqueous solution and subjected to extraction with chloroform. The organic solvent was washed with a saturated saline solution and then dried with anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified through silica gel column

chromatography (chloroform/methanol), thereby obtaining the subject compound (552.4 mg) as a yellow oily substance.

[0052]

Example 11-9: Synthesis of 5-cyano-2-(3-dipropylaminobutyl)-1-methoxymethoxy-indane

The compound (552 mg) obtained in Example 11-8 was dissolved in DMF (1.67 ml) and added with zinc cyanide (94.3 mg) and tetrakistriphenyl phosphine palladium (61.8 mg), followed by stirring at 80°C for 48 hours. The reaction solution was added with chloroform and washed with a 7% aqueous ammonium solution and a saturated saline solution. The resultant was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (436.8 mg) as a yellow oily substance.

[0053]

Example 11-10: Synthesis of 5-aminomethyl-2-(3-dipropylaminobutyl)-1-methoxymethoxy-indane

The compound (436 mg) obtained in Example 11-9 was dissolved in THF (21.8 ml) and added with lithium aluminum hydride (138.7 mg) and the whole was stirred at room temperature for 24 hours. The reaction solution was added with ethyl acetate, methanol, and a 10% aqueous potassium sodium tartrate solution, and the whole was stirred for 1 hour, followed by extraction with chloroform. The extract was washed with a saturated saline solution and then dried with anhydrous sodium sulfate, followed

by concentration under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (189.7 mg) as a yellow oily substance.

[0054]

Example 11-11: Synthesis of 2-[2-(4-dipropylaminobutyl)-1-methoxymethoxy-indan-5-ylmethyl]-isoindol-1,3-dione

The compound (189 mg) obtained in Example 11-10 was dissolved in DMF (5.6 ml) and added with potassium carbonate (108.5 mg) and carbethoxyphthalimide (172.0 mg) and the whole was stirred at room temperature for 3 hours. The reaction solution was added with water and subjected to extraction with chloroform. The extract was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (253 mg) as a yellow oily substance.
MS(FAB,Pos.):m/z=493$[M+H]^+$

Example 11-12: Synthesis of 2-[2-(4-dipropylamino-butyl)-3H-inden-5-ylmethyl]-isoindol]-1,3-dione

The compound (113.0 mg) obtained in Example 11-11 was dissolved in dioxane (2.2 ml) and the whole was stirred at room temperature for 24 hours. The reaction solution was concentrated under reduced pressure. The residue was dissolved in chloroform and washed with a saturated aqueous sodium hydrogen carbonate solution and then with a saturated saline solution. The resultant

was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (98.8 mg) as a yellow oily substance.
MS(FAB,Pos.):m/z=449[M+H]$^+$

Example 11-13: Synthesis of
[4-(6-aminomethyl-1H-inden-2-yl)-butyl]-dipropyl-amine

The compound (82.0 mg) obtained in Example 11-12 was dissolved in methanol (4.1 ml) and added with hydrazine monohydrate (0.082 ml) and the whole was refluxed under heating for 3 hours. The reaction solution was concentrated under reduced pressure. Then, the residue was added with water and subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (40.1 mg) as a yellow oily substance.
MS(FAB,Pos.):m/z=301[M+H]$^+$

Example 11-14: Synthesis of
[4-(6-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-1H-inden-2-yl)-butyl]-dipropyl-amine

The compound (40.1 mg) obtained in Example 11-13 was dissolved in methanol (2.0 ml) and added with 2-imidazole carboxaldehyde (19.2 mg) and trimethyl orthoformate (42.5 mg) and the whole was stirred at room temperature for 30 minutes. Subsequently, the solution was added with sodium borohydride (15.1

mg) under ice-cooling, followed by stirring at room temperature for additional 30 minutes. The reaction solution was concentrated under reduced pressure. The residue was added with water, and extracted with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (27.3 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=380$[M+H]^+$

Example 11-15: Synthesis of [4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1H-inden-2-yl)-butyl]-dipropyl-amine [Compound No. 11]

The compound (27.3 mg) obtained in Example 11-14 was dissolved in methanol (1.37 ml) and added with sodium cyanoborohydride (9.0 mg) and 1-methyl-2-imidazole carboxaldehyde (11.8 mg). The solution was adjusted to pH 4 by addition of acetic acid, followed by stirring at room temperature for 3 hours. Then, the reaction solution was concentrated under reduced pressure. The residue was dissolved in chloroform, washed with a saturated aqueous sodium hydrogen carbonate solution, and dried with anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (31.5 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=475$[M+H]^+$

^{1}H-NMR(500Mz,DMSO-d_6+D_2O):δ=0.90(6H,t,J=7.3Hz),1.60-1.68(8H,m),2.96-3.31(8H,m),3.69(5H,m),4.01-4.15(6H,m),6.52(1H,s),7.05-7.62(7H,m).

[Example 12]

[0055]

Production example 12: Synthesis of 1-(4-dipropylaminobutyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-urea

[Compound No. 12]

Example 12-1: Synthesis of 1-(4-cyano-phenyl)-3-(4-dipropylaminobutyl)-urea

The compound (581.4 mg) obtained in Example 1-2 was dissolved in anhydrous toluene (17 ml) and then added with 4-vinylidene aminobenzonitrile (manufactured by Aldrich Corporation) (485.7 mg) and the whole was stirred at room temperature for 1.5 hours. After completion of the reaction, the solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (478 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=317[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.88(6H,t,J=7.3Hz),1.43-1.59(8H,m),2.37-2.44(6H,m),3.25(2H,dd,J=6.1,11.2Hz),6.06(1H,br),6.90(1H,br),7.48(2H,d,J=8.8Hz),7.54(2H,d,J=8.8Hz).

Example 12-2: Synthesis of 1-(4-aminomethylmethylphenyl)-3-(4-dipropylaminobutyl)-urea

The compound (466.4 mg) obtained in Example 12-1 was dissolved in anhydrous THF (14 ml) and the whole was cooled with

ice. Lithium aluminum hydride (223.1 mg) was added thereto and the whole was stirred at room temperature for 2.5 hours. After the reaction has been stopped by addition of ethyl acetate, an aqueous potassium sodium tartrate solution was added thereto and the whole was stirred, followed by extraction with chloroform. The extract was washed with a saturated saline solution and dried with magnesium sulfate. The solvent was distilled off and the residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (195 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=321[M+H]$^+$

Example 12-3: Synthesis of 1-(4-dipropylaminobutyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-urea

The compound (195.6 mg) obtained in Example 12-2 was dissolved in anhydrous methanol (7.8 ml) and added with 2-imidazole carboxaldehyde (88.4 mg) and trimethyl orthoformate (0.200 ml) and the whole was stirred at room temperature for 14 hours. Then, the solution was added with sodium borohydride (69.2 mg) and stirred at room temperature for 1.5 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The resultant was added with water and subjected to extraction with chloroform. The extract was washed with a saturated saline solution and dried with magnesium sulfate. The solvent was distilled off and the residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (101 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=401[M+H]$^+$

Example 12-4:

1-(4-dipropylaminobutyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-urea

[Compound No. 12]

The compound (101 mg) obtained in Example 12-3 was dissolved in anhydrous methanol (4.0 ml) and added with 1-methyl-2-imidazole carboxaldehyde (41.8 mg) and sodium cyanoborohydride (47.1 mg). The solution was adjusted to pH 5 by addition of acetic acid, followed by stirring at room temperature for 20 hours. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution and subjected to extraction with chloroform. The extract was dried with magnesium sulfate and the solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (80.3 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=495$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.89(6H,t,J=7.3Hz),1.46(2H,quint.,J=6.9Hz),1.63-1.69(6H,m),2.94-2.99(4H,m),3.01-3.06(2H,m),3.09(2H,m),3.57(2H,s),3.69(3H,s),4.04(2H,s),4.11(2H,s),6.64(1H,br),7.20(2H,d,J=8.7Hz),7.30(2H,d,J=8.7Hz),7.55(2H,dd,J=2.0,6.4Hz),7.64(2H,s),9.01(1H,brs),10.09(1H,br),14.67-14.74(2H,br).

[Example 13]

[0056]

Production example 13: Synthesis of

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylm

ethyl)-amino]-methyl}-1-methyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 13]

Example 13-1: Synthesis of 4-amino-3-(5-t-butoxycarbonylamino-pentanoylamino)-benzoic acid methyl ester

In DMF (20 ml), 5-t-butoxycarbonylamino valeric acid (manufactured by Aldrich Corporation) (1.45 g), WSCI hydrochloride (1.74 g), and HOBt (1.25 g) were dissolved and the whole was stirred for 15 minutes. Then, the solution was added with methyl 3,4-diaminobenzoate (1.00 g) and stirred at room temperature for 4 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and then washed with a saturated aqueous ammonium chloride solution and a 1 mol/l sodium hydroxide aqueous solution. Subsequently, the resultant was subjected to extraction with chloroform and the extract was then washed with a saturated saline solution, followed by drying with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (1.46 g).

MS(FAB,Pos.):m/z=365$[M+H]^+$

Example 13-2: Synthesis of 2-(4-amino-butyl)-3-methyl-3H-benzimidazol-5-carboxylic acid methyl ester

The compound (366 mg) obtained in Example 13-1 was dissolved in DMF (7.0 ml) and then added with 60% sodium hydride (44.3 mg) and the whole was stirred for 1 hour. Subsequently, methyl iodide

(222 μl) was gradually added thereto and the whole was stirred at room temperature for 2 hours. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was dissolved in chloroform. The resultant was washed with saturated sodium hydrogen carbonate and subjected to extraction with chloroform. After having been washed with a saturated saline solution, the extract was dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure.

The resultant was dissolved in methanol (5.0 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (5.0 ml), followed by stirring at room temperature for 2 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. Then, the residue was dissolved in chloroform and washed with a 1 mol/l sodium hydroxide aqueous solution, followed by extraction with chloroform. The extract was washed with a saturated saline solution and dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure, thereby obtaining the subject compound (218.9 mg) as a pale-brown oily substance.

MS(FAB,Pos.):m/z=262$[M+H]^+$

Example 13-3: Synthesis of 2-(4-dipropylamino-butyl)-3-methyl-3H-benzimidazol-5-carboxylic acid methyl ester

The compound (219 mg) obtained in Example 13-2 was dissolved in methanol (4.2 ml). The solution was added with acetic acid (200 μl), sodium cyanoborohydride (170.9 mg), and gradually added with propionaldehyde (180 μl) and the whole was stirred at room

temperature for 2 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. Then, the residue was dissolved in chloroform and washed with a 1 mol/l sodium hydroxide aqueous solution, followed by extraction with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure, thereby obtaining the subject compound (305 mg) as a brown oily substance.

MS(FAB,Pos.):m/z=346$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.82(6H,t,J=7.3Hz),1.37(4H,sext.,J=7.3Hz),1.51(4H,quint.,J=7.3Hz),1.78(4H,quint.,J=7.6Hz),2.26-2.37(4H,br),2.40-2.49(2H,br),2.89-2.94(2H,m),3.81(3H,s),3.88(3H,s),7.62(1H,d,J=8.3Hz),7.80(1H,d,J=8.3Hz),8.13(1H,s).

Example 13-4: Synthesis of [2-(4-dipropylamino-butyl)-3-methyl-3H-benzimidazol-5-yl]-methanol

Lithium aluminum hydride (120 mg) was suspended in THF (3.0 ml) and then cooled to 0°C. After that, a solution of the compound (305 mg) obtained in Example 13-3 in THF (4.5 ml) was dropped in the suspension. The whole was warmed back to room temperature and stirred for 2 hours. After completion of the reaction, sodium sulfate decahydrate was gradually added to the solution until bubbling was stopped, and a 1 mol/l sodium hydroxide aqueous solution was then added to the mixture until a white precipitate was generated. Solid matter was separated by filtration and the solvent was then distilled off from the filtrate under reduced pressure. The residue was purified through silica gel column

chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (246 mg) as a brown oily substance.
MS(FAB,Pos.):m/z=318$[M+H]^+$

Example 13-5: Synthesis of 2-[2-(4-dipropylamino-butyl)-3-methyl-3H-benzimidazol-5-ylmethyl]-isoindol-1,3-dione

The compound (245 mg) obtained in Example 13-4 was dissolved in chloroform (5.0 ml). The solution was added with methanesulfonyl chloride (177 mg) and triethylamine (107 µl), followed by stirring at room temperature for 2 hours. Then, lithium chloride (65.2 mg) was added thereto and the whole was stirred overnight. After completion of the reaction, the solution was washed with a saturated aqueous sodium hydrogen carbonate solution and subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. The solvent was distilled off.

The resultant was dissolved in DMF (3.0 ml) and added with potassium phthalimide (164 mg), followed by stirring at room temperature for 3 days.

After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and washed with water, followed by extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate.

After filtration, the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol/water), thereby

obtaining the subject compound (232 mg) as a pale-yellow solid.
MS(FAB,Pos.):m/z=447[M+H]$^+$

Example 13-6: Synthesis of
[4-(6-aminomethyl-1-methyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine

The compound (232 mg) obtained in Example 13-5 was dissolved in a 40% methylamine/methanol solution (3.0 ml) and the whole was stirred at room temperature for 20 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and then washed with a 1 mol/l sodium hydroxide aqueous solution, followed by extraction with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol/water), thereby obtaining the subject compound (17.0 mg) as a pale-yellow oily substance.
MS(FAB,Pos.):m/z=317[M+H]$^+$

Example 13-7: Synthesis of
[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-methyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 13]

The compound (17.0 mg) obtained in Example 13-6 was dissolved in methanol (0.5 ml) and added with trimethyl orthoformate (20 µl) and 2-imidazole carboxaldehyde (6.4 mg) and the whole was stirred at room temperature for 1 hour. After having been cooled

to 0°C, the solution was added with sodium borohydride (6.0 mg) and warmed back to room temperature, followed by stirring for 30 minutes. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was then dissolved in chloroform and washed with a saturated aqueous sodium hydrogen carbonate solution, followed by extraction with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure.

The resultant was dissolved in methanol (1.0 ml). The solution was added with 1-methyl-2-imidazole carboxaldehyde (18.0 mg), acetic acid (20 μl), and sodium cyanoborohydride (12.5 mg) and the whole was stirred at room temperature for 1 hour. After completion of the reaction, the solvent was distilled off under reduced pressure. Then, the residue was dissolved in chloroform and washed with a saturated aqueous sodium hydrogen carbonate solution, followed by extraction with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. Then, the residue was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (19.2 mg) of the subject compound as a pale-yellow solid.

MS(FAB,Pos.):m/z=491[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.91(6H,t,J=7.3Hz),1.67-1.71(4H,m),1.76-1.86(2H,m),1.87-1.96(2H,m),2.96-3.04(2H,m),3.08-3.14(2H,m),3.25(2H,t,J=7.3Hz),3.74(3H,s),3.89(2H,s),4.07(3H,s),4.13(2H,s),4.21(2H,s),7.51-7.54(3H,m),7.63(2H,s),7.68(1H,d,J=8.4H

z),8.29(1H,s).

[Example 14]

[0057]

Production example 14: Synthesis of 3-(3-dipropylaminopropyl)-8-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-3,4-dihydro-1H-benzo[e][1,4]diazepin-2,5-dione [Compound No. 14]

Example 14-1: Synthesis of 2-[5-t-butoxycarbonylamino-2-(9H-fluoren-9-ylmethoxycarbonylamino)-pentanoylamino]-terephthalic acid dimethyl ester

In anhydrous pyridine (30 ml), 2-amino-terephthalic acid dimethyl ester (manufactured by Merck Ltd.) (1.46 g) and 5-t-butoxycarbonylamino-2-(9H-fluoren-9-ylmethoxycarbonylamino)-valeric acid (manufactured by Watanabe Chemical Industries, Ltd.) (3.18 g) were dissolved. The whole was cooled to -15°C and added with phosphorus oxychloride (0.718 ml), followed by stirring at room temperature for 1 hour. After completion of the reaction, the whole was poured in ice-cold water and subjected to extraction with ethyl acetate. The extract was washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution and dried with magnesium sulfate. After the solvent was distilled off, the resultant was subjected to azeotropic distillation with toluene. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (3.33 g) as a white crystal.

MS(FAB,Pos.):m/z=646$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=1.44(9H,s),1.62-1.64(2H,m),1.79-1.84(1

H,m),2.06-2.18(1H,m),3.20-3.21(2H,br),3.83(3H,s),3.95(3H,s),4.28(1H,t,J=7.1Hz),4.37(1H,t,J=7.3Hz),4.43(1H,d,J=5.1Hz),4.52(1H,dd,J=6.8,10.4Hz),5.21(1H,d,J=6.3Hz),7.32(2H,t,J=6.1Hz),7.40(2H,t,J=7.6Hz),7.66(2H,d,J=7.3Hz),7.70(2H,d,J=7.3Hz),7.77(3H,d,J=7.8Hz),8.10(1H,d,J=8.3Hz),9.32(1H,s),11.56(1H,s).

Example 14-2: Synthesis of 2-(2-amino-5-t-butoxycarbonylamino-pentanoylamino)-terephthalic acid dimethyl ester

The compound (236.0 mg) obtained in Example 14-1 was dissolved in anhydrous DMF (4.7 ml) and added with diethylamine (4.7 ml) and the whole was stirred at room temperature for 1 hour. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (194.7 mg) as a colorless viscous solid.

MS(FAB,Pos.):m/z=424$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=1.43(9H,s),1.64-1.72(4H,m),3.17-3.19(2H,m),3.58-3.61(1H,m),3.94(3H,s),3.97(3H,s),7.76(1H,dd,J=1.7,8.3Hz),8.02(1H,s),8.11(1H,d,J=8.1Hz),9.41(1H,s),12.08(1H,s).

Example 14-3: Synthesis of 3-(3-t-butoxycarbonylamino-propyl)-2,5-dioxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepin-8-carboxylic acid ethyl ester

The compound (303.8 mg) obtained in Example 14-2 and sodium t-butoxide (manufactured by Wako Pure Chemical Industries, Ltd.) (138.4 mg) were dissolved in anhydrous THF (6.0 ml) and the whole was stirred at 60°C for 15 hours. After completion of the reaction,

water was added thereto and the whole was subjected to extraction with chloroform.

The extract was dried with magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (36.6 mg) as a white solid.

MS(FAB,Pos.):m/z=392$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=1.41(9H,s),1.43(1H,br),1.65-1.82(2H,m),2.05-2.11(1H,m),3.18(2H,d,J=6.6Hz),3.77(1H,d,J=6.1Hz),3.96(3H,s),4.88(1H,brs),7.13(1H,brs),7.73(1H,s),7.90(1H,dd,J=1.5,8.0Hz),8.04(1H,d,J=8.3Hz),8.66(1H,brs).

Example 14-4: Synthesis of [3-(8-hydroxymethyl-2,5-dioxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepin-3-yl)-propyl]-carbamic acid t-butyl ester

The compound (35.1 mg) obtained in Example 14-3 was dissolved in anhydrous THF (1.0 ml) and added with Lithium aluminum hydride (6.8 mg) and the whole was stirred at room temperature for 30 minutes. After completion of the reaction, an aqueous potassium sodium tartrate solution was added thereto and the whole was vigorously stirred at room temperature, followed by extraction with chloroform. The extract was dried with magnesium sulfate and the solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (16.9 mg) as a white solid.

MS(FAB,Pos.):m/z=364$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.90(1H,d,J=6.3Hz),1.42(9H,s),1.62(2H,br),2.03-2.05(1H,m),3.14-3.15(2H,m),3.68(1H,dd,J=5.6,11.7Hz)

,4.70(2H,t,J=3.9Hz),6.87-6.96(1H,m),7.04(1H,d,J=6.6Hz),7.11(1H,d,J=7.3Hz),7.83(1H,d,J=8.1Hz),8.94(1H,br).

Example 14-5: Synthesis of 3-(3-dipropylaminopropyl)-8-hydroxymethyl-3,4-dihydro-1H-benzo[e][1,4]diazepin-2,5-dione

The compound (224 mg) obtained in Example 14-4 was dissolved in methanol (2.2 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (2.2 ml), and the whole was stirred at room temperature for 1 hour. After completion of the reaction, the solvent was distilled off under reduced pressure. The resultant was treated with an anion-exchange resin (Amberlite IRA-410).

The resultant was dissolved in anhydrous methanol (5.1 ml) and added with propionaldehyde (0.104 ml), trimethyl orthoformate (0.158 ml), and sodium cyanoborohydride (121 mg) and the whole was stirred at room temperature for 21 hours.

After completion of the reaction, the solvent was distilled off under reduced pressure. The resultant was added with water and subjected to extraction with chloroform. The extract was dried with magnesium sulfate. The solvent was distilled off and the residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (36.0 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=348$[M+H]^+$

Example 14-6: Synthesis of 2-(1-methyl-1H-imidazol-2-ylmethyl)-isoindol-1,3-dione

The compound (83.50 g) obtained in Example 10-2 was suspended

in DMF (250 ml) and added with sodium t-butoxide (49.00 g) at -30°C. The solution was further added with a potassium phthalimide salt (95.0 g) and then the whole was stirred at 70°C for 2 hours. After completion of the reaction, the resultant was added into water (800 ml). The precipitated crystal was filtrated, washed with water, and dried, thereby obtaining the subject compound (101.5 g) as a white solid.

[0058]

Example 14-7: Synthesis of C-(1-methyl-1H-imidazol-2-yl)-methylamine

The compound (5.89 g) obtained in Example 14-6 was suspended in methanol (118 ml) and added with hydrazine monohydrate (1.89 ml), and the whole was refluxed under heating for 2.5 hours. After the solution was left for cooling, the precipitate was filtrated through Celite and the filtrate was distilled off under reduced pressure, thereby obtaining the subject compound (898.5 mg) as a yellow oily substance.

MS(EI):m/z=111$[M]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=1.99(2H,br),3.63(3H,s),3.90(2H,s),6.81(1H,d,J=1.2Hz),6.92(1H,d,J=1.2Hz).

Example 14-8: Synthesis of 3-(3-dipropylaminopropyl)-8-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-3,4-dihydro-1H-benzo[e][1,4]diazepin-2,5-dione [Compound No. 14]

The compound (36.0 mg) obtained in Example 14-5 was dissolved in chloroform (0.6 ml) and added with manganese dioxide (chemically processed product) (180 mg), and the whole was stirred at room

temperature for 3 hours. After completion of the reaction, the solution was filtrated through Celite and the solvent was distilled off. The resultant was dissolved in anhydrous methanol (1.4 ml) and added with the compound (16.7 mg) obtained in Example 14-7 and trimethyl orthoformate (0.033 ml), and the whole was stirred at room temperature for 16 hours. Sodium borohydride (11.3 mg) was added thereto and the whole was stirred at room temperature for 4 hours, followed by addition of water. The solvent was distilled off under reduced pressure, followed by extraction with chloroform. The extract was dried with magnesium sulfate and the solvent was distilled off under reduced pressure. The resultant was dissolved in anhydrous methanol (1.2 ml) and added with 2-imidazole carboxaldehyde (14.4 mg) and sodium cyanoborohydride (18.9 mg). The solution was adjusted to pH 5 with acetic acid and stirred at room temperature for 2 days. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution and subjected to extraction with chloroform, followed by drying with magnesium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (19.4 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=521$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6+D_2O):δ=0.87-0.90(6H,m),1.61-1.64(4H,m),1.79-1.83(4H,m),2.96-3.00(4H,m),3.07-3.08(2H,m),3.76(3H,s),4.03(1H,br),4.10(2H,br),4.24(4H,s),7.53-7.55(1H,m),7.61-7.63(4H,m),7.65(2H,s).

[Example 15]

[0059]

Production example 15: Synthesis of 4-{[(3,5-dimethyl-pyridin-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-N-(4-dipropylaminomethyl-phenyl)-benzamide [Compound No. 15]

Example 15-1: Synthesis of (4-nitro-benzyl)-dipropyl-amine

4-Nitrobenzylamine hydrochloride was subjected to desalting, thereby obtaining a free compound (3.94 g). The free compound was dissolved in anhydrous methanol (80 ml) and added with sodium cyanoborohydride (5.88 g), trimethyl orthoformate (7.18 ml), and propionaldehyde (4.67 ml), and the whole was stirred at room temperature for 2 hours under a nitrogen atmosphere. After completion of the reaction, the solvent was distilled off. The resultant was dissolved in chloroform and added with a saturated aqueous sodium hydrogen carbonate solution, and the whole was stirred for a while. The resultant was subjected to extraction with chloroform and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (2.61 g) as a yellow oily substance.

MS(FAB,Pos.):m/z=237$[M+H]^+$

Example 15-2: Synthesis of 4-dipropylaminomethyl-aniline

The compound (2.61 g) obtained in Example 15-1 was dissolved in methanol (25 ml). The solution was added with THF (13 ml), activated carbon (261 mg), and iron trichloride hexahydrate (26.1

mg) and the whole was refluxed for 30 minutes. After having been cooled to room temperature, the solution was added with hydrazine monohydrate (1.88 ml) and then the whole was refluxed for 3 hours. After completion of the reaction, the resultant was subjected to filtration through Celite. The filtrate was subjected to extraction with chloroform and washed with distilled water and a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate and the solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (865 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=207$[M+H]^+$

Example 15-3: Synthesis of [4-(4-dipropylaminomethyl-phenylcarbamoyl)-benzyl]-carbamic acid t-butyl ester

Commercially available 4-(t-butoxycarbonylamino-methyl)-benzoic acid (manufactured by Watanabe Chemical Industries, Ltd.) (1.16 g) was dissolved in chloroform (20 ml) and then added with WSCI hydrochloride (1.21 g), HOBt (963 mg), and the compound (865 mg) obtained in Example 15-2, and the whole was stirred overnight at room temperature. After completion of the reaction, a 1 mol/l sodium hydroxide aqueous solution was added thereto and the whole was stirred for a while. The solution was subjected to extraction with chloroform and washed with a saturated aqueous ammonium chloride solution, a saturated aqueous sodium hydrogen carbonate solution, and a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate and the solvent was distilled off. The

residue was then purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (545 mg) as a yellow solid.

MS(FAB,Pos.):m/z=440[M+H]$^+$

Example 15-4: Synthesis of 4-aminomethyl-N-(4-dipropylaminomethyl-phenyl)-benzamide

The compound (545 mg) obtained in Example 15-3 was dissolved in anhydrous methanol (10 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (10.0 ml), and the whole was stirred at room temperature for 1 hour. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution and subjected to extraction with chloroform, followed by washing with a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate and the solvent was distilled off, thereby obtaining the subject compound (389 mg) as a colorless crystal.

MS(FAB,Pos.):m/z=340[M+H]$^+$

Example 15-5: N-(4-dipropylaminomethyl-phenyl)-4-{[(1-methyl-1H-imidazol-2-ylmethyl)amino]methyl}-benzamide

The compound (389 mg) obtained in Example 15-4 was dissolved in anhydrous methanol (10 ml) and then added with trimethyl orthoformate (188 μl) and 2-imidazole carboxaldehyde (139 mg). The whole was stirred overnight at room temperature under a nitrogen atmosphere. Then, sodium borohydride (43.4 mg) was added thereto in an ice bath and the whole was stirred at room temperature for 2.5 hours. After completion of the reaction,

distilled water was added thereto and the whole was stirred for a while. The solution was subjected to extraction with chloroform and washed with a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate and the solvent was then distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (346 mg) as a yellow solid.

MS(FAB,Pos.):m/z=440$[M+H]^+$

Example 15-6: Synthesis of
3,5-dimethyl-pyridine-2-carboxaldehyde

In dichloromethane (15.0 ml), 2,3,5-trimethyl-pyridine (manufactured by Tokyo Kasei Kogyo Co., Ltd.) (1.29 g) was dissolved. After having been cooled to 0°C, the reaction solution was added with m-chloroperbenzoic acid (2.53 g), followed by stirring at room temperature for 1.5 hours. The reaction solution was added with a 1 mol/l sodium hydroxide aqueous solution and then subjected to extraction with chloroform. Subsequently, the organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The drying agent was filtrated out and the solvent was then distilled off, followed by dissolving the resultant residue in dichloromethane (25.0 ml). The reaction solution was added with trifluoroacetic anhydride (2.8 ml) and the whole was refluxed under heating for 3.5 hours. After the reaction solution was cooled to room temperature, the solvent was distilled off. The resultant residue was dissolved in methanol (60.0 ml). After having been cooled to 0°C, the reaction solution was added with a 12.5% sodium methoxide/methanol solution to adjust the solution to pH 10, and the whole was stirred

at room temperature for 16.5 hours. After the solvent was distilled off, the residue was added with distilled water and subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The drying agent was filtrated out and the solvent was then distilled off, followed by dissolving the residue in chloroform (30.0 ml). The reaction solution was added with manganese dioxide (chemically processed product) (6.10 g) and then stirred at room temperature for 18 hours. The reaction solution was filtrated through Celite. The solvent in the filtrate was distilled off and the resultant residue was then purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (1.14 g) as a yellow oily substance.

MS(FAB,Pos.):m/z=136$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=2.40(3H,s),2.63(3H,s),7.43(1H,brs),8.48(1H,brs),10.16(1H,s).

Example 15-7: Synthesis of 4-{[(3,5-dimethyl-pyridin-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-N-(4-dipropylaminomethyl-phenyl)-benzamide [Compound No. 15]

The compound (155 mg) obtained in Example 15-5 was dissolved in anhydrous methanol (3.0 ml) and added with sodium cyanoborohydride (33.7 mg), acetic acid (0.50 ml), and the compound (58.0 mg) obtained in Example 15-6, and the whole was stirred at room temperature for 2 days under a nitrogen atmosphere. After completion of the reaction, the solvent was distilled off. The resultant was dissolved in chloroform and added with a 1 mol/l

sodium hydroxide aqueous solution, followed by stirring for a while. Then, the solution was subjected to extraction with chloroform and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate and the solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (174 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=553$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6+D_2O):δ=0.88(6H,t,J=7.5Hz),1.65-1.76(4H,m),2.37(3H,s),2.40(3H,s),2.92-2.98(4H,m),3.75(3H,s),3.84(2H,s),4.16(2H,s),4.18(2H,s),4.28(2H,s),7.51(2H,d,J=8.4Hz),7.54(1H,d,J=2.0Hz),7.54-7.55(1H,m),7.56(1H,s),7.57(1H,d,J=2.1Hz),7.85(2H,d,J=8.5Hz),7.87(1H,s),7.88(1H,d,J=2.1Hz),8.16(1H,d,J=2.0Hz),8.53(1H,s).

[Example 16]

[0060]

Production example 16: Synthesis of 4-{[(5-ethyl-pyridin-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-N-(4-dipropylaminomethyl-phenyl)-benzamide [Compound No. 16]

Example 16-1: Synthesis of 5-ethyl-pyridine-2-carboxaldehyde

In dichloromethane (25.0 ml), 5-ethyl-2-methyl-pyridine (manufactured by Tokyo Kasei Kogyo Co., Ltd.) (2.31 g) was dissolved. After having been cooled to 0°C, the reaction solution was added with m-chloroperbenzoic acid (4.43 g) and the whole was stirred at room temperature for 2.5 hours. The reaction

solution was added with a 1 mol/l sodium hydroxide aqueous solution and then subjected to extraction with chloroform. Subsequently, the organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The drying agent was filtrated out and the solvent was then distilled off. The resultant was dissolved in dichloromethane (40.0 ml). The reaction solution was added with trifluoroacetic anhydride (5.6 ml) and the whole was refluxed under heating for 3.5 hours. After the reaction solution was cooled to room temperature, the solvent was distilled off. The resultant was dissolved in methanol (80.0 ml). After having been cooled to 0°C, the reaction solution was added with a 12.5% sodium methoxide/methanol solution to adjust the reaction solution to pH 10, followed by stirring at room temperature for 16.5 hours. After the solvent was distilled off, the residue was added with distilled water and subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The drying agent was filtrated out and the solvent was then distilled off. The resultant was dissolved in chloroform (50.0 ml). The reaction solution was added with manganese dioxide (chemically processed product) (7.44 g) and then stirred at room temperature for 18 hours. The reaction solution was filtrated through Celite. The solvent in the filtrate was distilled off and the resultant residue was then purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (515.6 mg) as a yellow oily substance.

MS(FAB,POS.):m/z=136$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=1.31(3H,t,J=7.6Hz),2.77(2H,q,J=7.6Hz),

7.70(1H,d,J=7.8Hz),7.91(1H,d,J=7.8Hz),10.06(1H,s).

Example 16-2: Synthesis of 4-{[(5-ethyl-pyridin-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-N-(4-dipropylaminomethyl-phenyl)-benzamide [Compound No. 16]

The compound (191 mg) obtained in Example 15-5 was dissolved in anhydrous methanol (4.0 ml) and added with sodium cyanoborohydride (41.5 mg), acetic acid (0.50 ml), and the compound (71.4 mg) obtained in Example 16-1 and the whole was stirred at room temperature for 2 days under a nitrogen atmosphere. After completion of the reaction, the solvent was distilled off. The resultant was dissolved in chloroform and added with a 1 mol/l sodium hydroxide aqueous solution, followed by stirring for a while. Then, the solution was subjected to extraction with chloroform and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate and the solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (222 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=553$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6+D_2O):δ=0.88(6H,t,J=7.3Hz),1.20(3H,t,J=7.6Hz),1.66-1.77(4H,m),2.77(2H,q,J=7.6Hz),2.91-2.98(4H,m),3.78(3H,s),3.86(2H,s),4.18(2H,s),4.22(2H,s),4.28(2H,s),7.51(2H,s),7.52(2H,d,J=8.4Hz),7.57(2H,d,J=8.7Hz),7.87(2H,d,J=8.2Hz),7.88(2H,d,J=8.7Hz),7.98(1H,d,J=8.2Hz),8.37(1H,dd,J=2.0,8.2Hz),8.68(1H,d,J=1.8Hz).

[Example 17]

[0061]

Production example 17: Synthesis of [4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-3,4-dihydro-1H-isoquinolin-2-yl)-butyl]-dipropyl-amine [Compound No. 17]

Example 17-1: Synthesis of 6-bromo-3,4-dihydro-2H-isoquinolin-1-one

In benzene (71 ml), 5-bromoindanone (5.47 g) was suspended. The solution was added with concentrated sulfuric acid (14 ml) and the whole was vigorously stirred. Then, the solution was gradually added with sodium azide (2.52 g), followed by stirring at room temperature for 30 minutes. The resultant was added with ethyl acetate, washed with water and a saturated saline solution, and dried with magnesium sulfate. The solvent was distilled off.

The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (2.25 g) as a white solid.

MS(FAB,Pos.):m/z=226,228$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=2.99(2H,t,J=6.8Hz),3.57(2H,dt,J=2.9,6.7Hz),6.23(1H,br),7.40(1H,s),7.50(1H,dd,J=2.0,8.3Hz),7.93(1H,d,J=8.3Hz).

Example 17-2: Synthesis of 1-(6-bromo-3,4-dihydro-1H-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone

The compound (2.253 g) obtained in Example 17-1 was dissolved in anhydrous THF (11 ml) and added with a 1 mol/l borane-THF

complex/THF solution (manufactured by Kanto Chemical Co., Inc.) (55.4 ml). The whole was refluxed overnight under heating. After the whole was left for cooling, methanol was added thereto and the solvent was distilled off. The resultant was added with 1 mol/l hydrochloric acid and refluxed under heating for 3 hours. After completion of the reaction, the solution was cooled with ice and added with a 1 mol/l sodium hydroxide aqueous solution and 27% ammonium water, followed by extraction with chloroform. The extract was dried with magnesium sulfate and the solvent was distilled off.

The resultant was dissolved in anhydrous dichloromethane (40 ml), added with triethylamine (1.53 ml), and cooled with ice. Trifluoroacetic anhydride (1.55 ml) was added thereto and the whole was stirred at room temperature for 1 hour. After completion of the reaction, the resultant was added with a saturated aqueous sodium hydrogen carbonate solution, subjected to extraction with chloroform, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure, thereby obtaining the subject compound (2.23 g) as a white solid.

MS(FAB,Pos.):m/z=308,310$[M+H]^+$

Example 17-3: Synthesis of
1,2,3,4-tetrahydro-isoquinolin-6-carbonitrile

The compound (2.23 g) obtained in Example 17-2 was dissolved in NMP (27 ml) and added with cuprous cyanide (1.56 g) and the whole was refluxed under heating for 4 hours. After completion of the reaction, the whole was cooled with ice and added with water and ammonium water. The resultant was subjected to extraction with chloroform and dried with magnesium sulfate. The

solvent was distilled off under reduced pressure. The resultant was dissolved in diethyl ether and added with a 4 mol/l hydrogen chloride/dioxane solution. The precipitate was filtrated and washed with diethyl ether. The resultant was dried under heating, thereby obtaining a hydrochloride (1.95 g) of the subject compound as a brown solid.

MS(FAB,Pos.):m/z=159[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=3.06(2H,t,J=6.4Hz),3.34-3.36(2H,m),4.32(2H,t,J=4.6Hz),7.45(1H,d,J=8.1Hz),7.71(1H,dd,J=1.7,7.8Hz),7.76(1H,s).

Example 17-4: Synthesis of (4,4-diethoxy-butyl)-dipropyl-amine

In anhydrous methanol (53 ml), 4,4-diethoxy-butylamine (manufactured by Aldrich Corporation) (1.33 g) was dissolved. The solution was added with propionaldehyde (1.23 ml), trimethyl orthoformate (2.45 ml), and sodium cyanoborohydride (1.40 g) and the whole was stirred at room temperature for 2 hours. After completion of the reaction, the solvent was distilled off. The resultant was added with water, subjected to extraction with chloroform, and dried with magnesium sulfate and the solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (1.03 g) as a colorless oily substance.

MS(FAB,Pos.):m/z=246[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.87(6H,t,J=7.3Hz),1.21(6Ht,J=7.0Hz),1.42-1.48(4H,m),1.49-1.54(2H,m),1.59-1.64(2H,m),2.36-2.39(4H,m),2.44(2H,t,J=7.5Hz),3.50(2H,quint.,J=7.1Hz),3.65(2H,quint.,J=7.1Hz),4.50(1H,t,J=5.6Hz).

Example 17-5: Synthesis of 4-dipropylamino-butylaldehyde

The compound (1.03 g) obtained in Example 17-4 was dissolved in THF (10 ml) and added with 1 mol/l hydrochloric acid (10 ml). The whole was stirred at room temperature for 17 hours and the solvent was distilled off. The solution was added with a 1 mol/l sodium hydroxide aqueous solution and subjected to extraction with chloroform. The extract was dried with magnesium sulfate and the solvent was distilled off, thereby obtaining the subject compound (697 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=172$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.6Hz),1.39-1.46(4H,m),1.77(2H,quint.,J=7.1Hz),2.32-2.36(4H,m),2.40-2.46(2H,m),9.76(1H,s).

Example 17-6: Synthesis of 2-(4-dipropylamino-butyl)-1,2,3,4-tetrahydro-isoquinolin-6-carbonitrile

The compound (439 mg) obtained in Example 17-3 was dissolved in a 1 mol/l sodium hydroxide aqueous solution. The whole was subjected to extraction with chloroform and dried with magnesium sulfate and the solvent was distilled off.

The resultant was dissolved in anhydrous dichloromethane (6.7 ml) and added with the compound (331 mg) obtained in Example 17-5 and sodium triacetoxyborohydride (1.23 g), and the whole was reacted at room temperature for 2 days. The resultant was added with a saturated aqueous sodium hydrogen carbonate solution, subjected to extraction with chloroform, and dried with magnesium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl

acetate), thereby obtaining the subject compound (220 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=314[M+H]$^+$

Example 17-7: Synthesis of [4-(6-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-3,4-dihydro-1H-isoquinolin-2-yl)-butyl]-dipropylamine

The compound (220 mg) obtained in Example 17-6 was dissolved in anhydrous THF (8.8 ml) and added with Lithium aluminum hydride (106 mg). The whole was stirred at room temperature for 2 hours. After completion of the reaction, the solution was added with ethyl acetate and an aqueous sodium potassium tartrate solution, and the whole was stirred, followed by extraction with chloroform. The extract was dried with magnesium sulfate and the solvent was distilled off.

The resultant was dissolved in anhydrous methanol (8.3 ml) and added with 2-imidazole carboxaldehyde (100 mg) and trimethyl orthoformate (0.23 ml), and the whole was stirred at room temperature for 16 hours. The solution was added with sodium borohydride (79.4 mg) and the whole was stirred at room temperature for 6 hours. The resultant was added with water, subjected to extraction with chloroform, and dried with magnesium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (104 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=398[M+H]$^+$

Example 17-8: Synthesis of

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-3,4-dihydro-1H-isoquinolin-2-yl)-butyl]-dipropyl-amine [Compound No. 17]

The compound (104 mg) obtained in Example 17-7 was dissolved in anhydrous methanol (4.0 ml) and added with 1-methyl-2-imidazole carboxaldehyde (42.9 mg) and sodium cyanoborohydride (49.0 mg). The solution was adjusted to pH 5 with acetic acid and stirred at room temperature for 16.5 hours. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution, subjected to extraction with chloroform, and dried with magnesium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (115 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=492$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6+D_2O):δ=0.92(6H,t,J=7.3Hz),1.64-1.70(4H,m),1.72-1.76(2H,m),1.85-1.86(2H,m),2.99-3.03(4H,m),3.08-3.12(2H,m),3.18-3.27(4H,m),3.68(3H,s),3.70(4H,s),4.09(2H,s),4.19(2H,s),4.20(1H,d,J=18.9Hz),4.45(1H,d,J=15.7Hz),7.06(1H,d,J=8.1Hz),7.17(1H,d,J=8.4Hz),7.21(1H,s),7.48(2H,s),7.60(2H,s).

[Example 18]

[0062]

Production example 18: Synthesis of [3-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-methyl-1H-benzimidazol-2-yl)-benzyl]-dipropyl-amine [Compound No. 18]

Example 18-1: Synthesis of 3-dipropylaminomethyl-benzoic acid

methyl ester

In DMF (12.5 ml), 3-bromomethyl benzoic acid methyl ester (831 mg) was dissolved. The solution was added with dipropylamine (971 µl) and the whole was stirred at room temperature for 2 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and washed with a saturated aqueous sodium hydrogen carbonate solution, followed by extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure, thereby obtaining the subject compound (858 mg) as a brown solid.

[0063]

Example 18-2: Synthesis of 3-dipropylaminomethyl-benzoic acid

The compound (858 mg) obtained in Example 18-1 was dissolved in methanol (18 ml) and added with a 1 mol/l sodium hydroxide aqueous solution (9.0 ml) and the whole was stirred overnight at room temperature. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in a 1 mol/l hydrochloric acid. After addition of chloroform, the resultant was added with sodium chloride to make the aqueous layer to be a saturated saline solution. The whole was subjected to extraction with chloroform and dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was dried under vacuum, thereby obtaining the subject compound (781 mg) as a white solid.

MS(FAB,Pos.):m/z=236$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.86(6H,t,J=7.3Hz),1.72(4H,sext.,J=7.3Hz),2.51(4H,quint.,J=1.8Hz),3.62(2H,s),4.40(3H,s),7.60(1H,d,J=7.8Hz),7.95(1H,d,J=7.0Hz),8.00(1H,d,J=7.8Hz),8.17(1H,s),10.70(1H,br).

Example 18-3: Synthesis of 4-amino-3-(3-dipropylaminomethyl-benzoylamino)-benzoic acid methyl ester

The compound (300 mg) obtained in Example 18-2, WSCI hydrochloride (365 mg), and HOBt (260 mg) were dissolved in chloroform (6.0 ml), and the whole was stirred for 1 hour. Then, 3,4-diaminobenzoic acid methyl ester (198 mg) was added thereto and the whole was stirred for 2 hours. A solid was precipitated, so DMF (2.0 ml) was added thereto and stirring was continued for additional 4 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. Then, the residue was dissolved in chloroform and washed with a saturated ammonium chloride aqueous solution, a saturated aqueous sodium hydrogen carbonate solution, and a saturated saline solution. Then, the resultant was dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (381 mg) as a brown oily substance.

MS(FAB,Pos.):m/z=384$[M+H]^+$

Example 18-4: Synthesis of 4-amino-3-[(3-dipropylaminomethyl-benzoyl)-methyl-amino]-benzoic acid methyl ester

The compound (380 mg) obtained in Example 18-3 was dissolved in DMF (7.6 ml) and 60% sodium hydride (60.0 mg) was added thereto, and the whole was stirred for 1 hour. After that, methyl iodide (213 mg) was gradually added thereto and the whole was stirred at room temperature for 2 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and washed with a saturated aqueous sodium hydrogen carbonate solution, followed by extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol/water), thereby obtaining the subject compound (83.0 mg) as a brown solid.

MS(FAB,Pos.):m/z=398$[M+H]^+$

Example 18-5: Synthesis of 2-(3-dipropylaminomethyl-phenyl)-3-methyl-3H-benzimidazol-5-carboxylic acid methyl ester

The compound (83.0 mg) obtained in Example 18-4 was dissolved in methanol (1.0 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (1.0 ml) and the whole was stirred at room temperature for 6 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in methanol to generate a free compound therefrom through an anion-exchange resin (Amberlite IRA-410). The resin was separated by filtration and the filtrate subjected to distillation of the solvent under reduced pressure. The residue was purified through silica gel column chromatography

(chloroform/ethyl acetate), thereby obtaining the subject compound (44.0 mg) as a brown solid.

MS(FAB,Pos.):m/z=380[M+H]$^+$

[0064]

Example 18-6: Synthesis of 2-(3-dipropylaminomethyl-phenyl)-3-methyl-3H-benzimidazol-5-carbaldehyde

Lithium aluminum hydride (16.5 mg) was suspended in THF (1.2 ml) and then the whole was cooled to 0°C. After that, a THF solution (1.0 ml) containing the compound (44.0 mg) obtained in Example 18-5 was dropped in the suspension. The whole was stirred at 0°C for 2 hours. After completion of the reaction, sodium sulfate decahydrate was gradually added to the solution until bubbling was stopped, and a 1 mol/l sodium hydroxide aqueous solution was then added to the mixture until a white precipitate was generated. A solid was separated by filtration and the filtrate was then subjected to distillation of the solvent under reduced pressure.

The resultant was dissolved in dichloromethane (1.0 ml) and added with manganese dioxide (chemically processed product) (105 mg) and the whole was stirred at room temperature for 19 hours. After completion of the reaction, the resultant was subjected to filtration through Celite and the filtrate was subjected to distillation of the solvent under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (28.0 mg) as a brown solid.

MS(FAB,Pos.):m/z=350[M+H]$^+$

Example 18-7: Synthesis of [3-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-methyl-1H-benzimidazol-2-yl)-benzyl]-dipropyl-amine [Compound No. 18]

The compound (31.2 mg) obtained in Example 18-6 was dissolved in methanol (1.0 ml) and added with acetic acid (30 μl) and 1-methyl-2-aminomethylimidazole (15.4 mg), and the whole was stirred at room temperature for 2 hours. Sodium cyanoborohydride (22.7 mg) was added thereto and the whole was stirred at room temperature for 15 hours. Furthermore, 2-imidazole carboxaldehyde (18.0 mg) was added thereto and the whole was stirred at room temperature for 18 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform, washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution, and dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (25.6 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=525$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.88(6H,t,J=7.3Hz),1.70-1.83(4H,m),2.97-3.07(4H,br),3.75(3H,s),3.93(2H,s),4.15(2H,s),4.17(3H,s),4.23(2H,s),4.47(2H,d,J=4.9Hz),7.54-7.55(2H,m),7.57(1H,d,J=8.3Hz),7.65(2H,s),7.74(1H,d,J=8.3Hz),7.81(1H,t,J=8.1Hz),7.99(1H,d,J=8.1Hz),8.03(1H,d,J=7.8Hz),8.32(1H,s),8.40(1H,s).

[Example 19]

[0065]

Production example 19: Synthesis of 6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridine-2-carboxylic acid-(4-dipropylamino-butyl)-amide [Compound No. 19]

Example 19-1: Synthesis of 6-cyano-imidazo[1,2-a]pyridine-2-carboxylic acid ethyl ester

In ethanol (30 ml), 2-amino-5-cyanopyridine (2.45 g) was dissolved. The solution was added with 3-bromo-2-oxo-propionic acid ethyl ester (3.90 g) and the whole was refluxed under heating for 7 hours. The concentrated residue was dissolved in a minimum amount of a 10% hydrogen chloride/methanol solution and the solution was adjusted to pH 8 with a saturated aqueous sodium hydrogen carbonate solution. The precipitate was collected by filtration, thereby obtaining the subject compound (3.81 g) as a pale-yellow solid.

MS(FAB,Pos.):m/z=216$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=1.33(3H,t,J=7.1Hz),4.33(2H,q,J=7.1Hz),7.61(1H,dd,J=1.7,9.6Hz),7.81(1H,ddd,J=0.7,1.0,9.6Hz),8.61(1H,d,J=0.7Hz),9.36(1H,dd,J=1.0,1.7Hz).

Example 19-2: Synthesis of 6-cyano-imidazo[1,2-a]pyridine-2-carboxylic acid-(4-dipropylamino-butyl)-amide

The compound (263 mg) obtained in Example 1-2 was dissolved in dichloromethane (4.0 ml) and a 15% trimethyl aluminum/hexane solution (1.08 ml) was dropped thereto. The whole was stirred

at room temperature for 15 minutes. The solution was added with the compound (300 mg) obtained in Example 19-1 and stirred for additional 20 hours. The resultant was heated to 40°C and stirred for additional 7 hours, and then 1 mol/l hydrochloric acid was added to stop the reaction, followed by extraction with chloroform. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution, water, and a saturated saline solution and dried with anhydrous sodium sulfate. The residue obtained by distilling the solvent off was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (237 mg) as a yellow solid.

MS(FAB,Pos.):m/z=342$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.87(6H,t,J=3.7Hz),1.43-1.73(8H,m),2.39-2.50(6H,m),3.50(2H,dd,J=6.3,6.8Hz),7.35(1H,dd,J=1.7,9.6Hz),7.51(1H,br),7.66(1H,ddd,J=0.7,1.0,9.6Hz),8.26(1H,d,J=0.5Hz),8.64(1H,dd,J=1.0,1.7Hz).

Example 19-3: Synthesis of 6-aminomethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridine-2-carboxylic acid-(4-dipropylamino-butyl)-amide

An ethanol solution (20 ml) containing the compound (40.2 mg) obtained in Example 19-2 was added with an ethanol suspension of Raney nickel and a 1 mol/l sodium hydroxide aqueous solution (2.0 ml), and the whole was stirred at room temperature for 14 hours under a hydrogen atmosphere. The catalyst was removed by filtration through Celite. The residue obtained by distilling the solvent off under reduced pressure was dissolved in chloroform, washed with water and a saturated saline solution, and dried with anhydrous sodium sulfate. The solvent was distilled off, thereby

obtaining the subject compound (40.1 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=350[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.5Hz),2.03-2.13(2H,br),2.34-2.38(4H,m),2.44(2H,t,J=7.2Hz),2.75-2.82(2H,m),2.85(2H,dd,J=6.2,12.4Hz),2.97(1H,ddd,J=3.5,5.5,16.9Hz),3.40(2H,dd,J=6.8,13.4Hz),3.67(1H,dd,J=10.3,12.2Hz),4.18(1H,ddd,J=1.1,5.2,12.4Hz),7.06(1H,br),7.40(1H,s).

Example 19-4:

6-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridine-2-carboxylic acid-(4-dipropylamino-butyl)-amide

The compound (28.3 mg) obtained in Example 19-3 was dissolved in methanol (1.0 ml) and added with trimethyl orthoformate (0.030 ml) and 2-imidazole carboxaldehyde (11.7 mg), and the whole was stirred at room temperature for 3 hours. After having been cooled to 0°C, the solution was added with sodium borohydride (4.6 mg) and the whole was warmed to room temperature and stirred for additional 15 minutes. The resultant was added with water to stop the reaction and subjected to extraction with chloroform. The organic layer was washed with water and a saturated saline solution and dried with anhydrous sodium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (30.5 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=430[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.85(6H,t,J=7.2Hz),1.41-1.48(6H,m),1.5

0-1.52(2H,m),1.56-1.59(2H,m),2.04-2.11(2H,br),2.33-2.36(4H,m),2.41(2H,t,J=7.3Hz),2.61(1H,dd,J=8.1,12.0Hz),2.70-2.76(2H,m),2.91(1H,ddd,J=3.6,5.5,16.9Hz),3.38(2H,dd,J=6.8,13.4Hz),3.61(1H,dd,J=10.0,12.4Hz),3.91(2H,d,J=2.2Hz),4.12(1H,dd,J=5.0,12.4Hz),7.00(2H,s),7.14(1H,br),7.31(1H,s).

Example 19-5: Synthesis of 6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridine-2-carboxylic acid-(4-dipropylamino-butyl)-amide [Compound No. 19]

The compound (19.6 mg) obtained in Example 19-4 was dissolved in methanol (2.0 ml) and added with 1-methyl-2-imidazole carboxaldehyde (6.2 mg) and sodium cyanoborohydride (5.9 mg). The solution was adjusted to pH 4 with acetic acid and stirred at room temperature for 3 hours. The resultant was added with a saturated sodium hydrogen carbonate aqueous solution to stop the reaction and subjected to extraction with chloroform. The organic layer was washed with water and a saturated saline solution and dried with anhydrous sodium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (22.0 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=524 $[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.87(6H,t,J=7.3Hz),1.40-1.69(9H,m),2.05(4H,br),2.13-2.18(1H,m),2.35(2H,d,J=4.5Hz),2.35(2H,t,J=7.8Hz),2.42(2H,t,J=7.3Hz),2.50-2.60(3H,m),2.80-2.84(1H,m),2.93-2.97(1H,m),3.40(2H,dd,J=6.6,13.4Hz),3.47-3.49(2H,m),3.56(2H,d

,J=2.7Hz),3.62-3.66(2H,m),3.73(3H,s),4.18(1H,dd,J=4.0,12.5Hz),6.95(1H,d,J=1.2Hz),7.03-7.04(3H,m),7.39(1H,s),12.39(1H,br).

[Example 20]

[0066]

Production example 20: Synthesis of N-(4-dipropylamino-butyl)-4-{[(1-methyl-1H-imidazo-2-ylmethyl)-(5-methyl-pyridin-2-ylmethyl)-amino]-methyl}-benzamide

[Compound No. 20]

Example 20-1: Synthesis of t-butyl-4-(4-{dipropylamino}butylcarbamoyl)benzyl carbamate

4-(t-butoxycarbonylamino-methyl)-benzoic acid (558 mg) was dissolved in chloroform (9.0 ml) and then added with WSCI hydrochloride (728 mg) and HOBt (503 mg) under ice-cooling, followed by stirring for 15 minutes. Then, a chloroform solution (3.0 ml) containing the compound (652 mg) obtained in Example 1-2 was gradually added thereto and the whole was stirred at room temperature for 12 hours. After completion of the reaction, a 1 mol/l hydrochloric acid (7.0 ml) was added thereto and the aqueous layer was extracted with chloroform. The organic layer was washed with a 1 mol/l sodium hydroxide aqueous solution and a saturated saline solution and dried with anhydrous sodium sulfate. The solvent was distilled off. The residue was then purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (715 mg) as a yellow oily substance.

[0067]

Example 20-2: Synthesis of 4-(aminomethyl)-N-(4-{dipropylamino}butyl)benzamide

The compound (715 mg) obtained in Example 20-1 was dissolved in methanol (7.0 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (7.0 ml) at room temperature and the whole was stirred for 2 hours. After completion of the reaction, the solvent was distilled off and the residue was dissolved in chloroform and washed with a 1 mol/l sodium hydroxide aqueous solution. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (559 mg) as a yellow oily substance.

[0068]

Example 20-3: Synthesis of N-(4-dipropylamino-butyl)-4-{[(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzamide

The compound (538 mg) obtained in Example 20-2 was dissolved in anhydrous methanol (10 ml), added with trimethyl orthoformate (600 μl) at room temperature under a nitrogen atmosphere, and then added with a methanol solution (2.0 ml) containing 1-methyl-2-imidazole carboxaldehyde (240 mg). The whole was stirred at room temperature for 36 hours and then added with sodium borohydride (140 mg) under ice-cooling. The whole was warmed to room temperature and stirred for 1 hour. After completion of the reaction, the resultant was added with water under ice-cooling while the whole was stirred. The solvent was distilled off under reduced pressure and the residue was dissolved in chloroform and added with water, followed by extraction of the aqueous layer with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium

sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (782 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=400$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.85(6H,t,J=7.4Hz),1.39-1.45(4H,m),1.56(2H,quint.,J=6.9Hz),1.65(2H,quint,J=6.9Hz),2.36(4H,t,J=2.2Hz),2.44(2H,t,J=6.9Hz),3.45(2H,dt,J=6.6,6.6Hz),3.63(3H,s),3.83(2H,s),3.87(2H,s),6.78(1H,brs),6.82(1H,d,J=1.2Hz),6.94(1H,d,J=1.2Hz),7.40(2H,d,J=8.1Hz),7.71(1H,dd,J=1.7,3.8Hz),7.28(1H,dd,J=1.7,3.8Hz).

Example 20-4: Synthesis of 5-methyl-2-pyridine aldehyde

The subject compound (439 mg) was obtained in a similar manner as in Example 15-6 except for using 2,5-lutidine as a raw material.

MS(FAB,Pos.):m/z=122$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=2.46(3H,s),7.67(1H,dd,J=1.4,7.9Hz),7.89(1H,d,J=7.9Hz),8.62(1H,d,J=1.4Hz),10.05(1H,s).

Example 20-5: Synthesis of N-(4-dipropylamino-butyl)-4-{[(1-methyl-1H-imidazol-2-ylmethyl)-(5-methyl-pyridin-2-ylmethyl)-amino]-methyl}-benzamide [Compound No. 20]

The compound (782 mg) obtained in Example 20-3 was dissolved in anhydrous methanol (12 ml) and then added with sodium cyanoborohydride (380 mg) and acetic acid (1.5 ml). Then, the solution was added with a methanol solution (2.0 ml) containing the compound (289 mg) obtained in Example 20-4 at -10°C and then

stirred at room temperature for 12 hours under a nitrogen atmosphere. After completion of the reaction, water was added thereto to stop the reaction. The solvent was distilled off under reduced pressure and chloroform and a 1 mol/l sodium hydroxide aqueous solution were added to the residue to make the pH of the aqueous layer about 10, followed by extraction of the aqueous layer with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The resultant was then concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and then treated with hydrochloric acid, thereby obtaining a hydrochloride (316 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=505$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.83(6H,t,J=7.3Hz),2.41(4H,qt,J=2.4,6.4Hz),1.55(2H,quint.,J=7.1Hz),1.65(2H,quint.,J=7.3Hz),2.32(3H,s),2.35(4H,t,J=2.4Hz),2.44(2H,t,J=7.1Hz),3.45(2H,dt,J=5.6,6.8Hz),3.49(3H,s),3.65(3H,s),3.69(2H,s),3.70(2H,s),6.94(1H,brt,J=5.0Hz),6.77(1H,d,J=1.2Hz),6.90(1H,d,J=1.2Hz),7.24(1H,d,J=7.8Hz),7.38(2H,d,J=8.3Hz),7.46(1H,dd,J=1.7,8.0Hz),7.69(2H,d,J=8.6Hz),8.37(1H,d,J=1.5Hz).

[Example 21]

[0069]

Production example 21: Synthesis of N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-methanesulfonamide [Compound No. 21]

Example 21-1: Synthesis of

4-{[t-butoxycarbonyl-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzoic acid methyl ester

In DMF (150 ml), 4-{[t-butoxycarbonyl-(1H-imidazol-2-ylmethyl)-amino]-methyl} benzoic acid (5.0 g) obtained by a known technique is dissolved. The solution was added with 60% sodium hydride (1.45 g) and methyl iodide (2.70 ml), and the whole was stirred at room temperature for 18 hours. The reaction solution was added to a saturated ammonium chloride aqueous solution and the whole was subjected to extraction with chloroform. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (2.31 g) as a brown solid.

MS(FAB,Pos.):m/z=360$[M+H]^+$

Example 21-2: Synthesis of (4-hydroxymethylbenzyl)-(1-methyl-1H-imidazol-2-ylmethyl)-carbamic acid t-butyl ester

Lithium aluminum hydride (1.0 g) was suspended in THF (95 ml). After that, a THF solution (95.1 ml) containing the compound (3.17 g) obtained in Example 21-1 was gradually dropped therein at room temperature. Then, the whole was stirred for additional 1 hour. The reaction solution was added with ethyl acetate, methanol, and a 10% aqueous sodium potassium tartrate solution and the whole was stirred for 1 hour, followed by extraction with chloroform. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified through silica gel column chromatography

(chloroform/methanol), thereby obtaining the subject compound (1.37 g) as a brown oily substance.

MS(FAB,Pos.):m/z=360[M+H]$^+$

Example 21-3: Synthesis of (4-formyl-1-benzyl)-(1-methyl-1H-imidazol-2-ylmethyl)-carbamic acid t-butyl ester

The compound (1.37 g) obtained in Example 21-2 was dissolved in ethyl acetate (68.5 ml) and then added with manganese dioxide (chemically processed product) (13.7 g) and the whole was stirred at room temperature for 1 hour. The reaction solution was filtrated through Celite. The filtrate was concentrated under reduced pressure. The residue was then purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (1.37 g) as a brown oily substance.

MS(FAB,Pos.):m/z=485[M+H]$^+$

Example 21-4: Synthesis of {4-[(4-dipropylaminobutylamino)-methyl]-benzyl}-(1-methyl-1H-imidazol-2-ylmethyl)-carbamic acid t-butyl ester

The compound (1.28 g) obtained in Example 21-3 was dissolved in methanol (38.6 ml). Then, the solution was added with the compound (0.669 g) obtained in Example 1-2 and trimethyl orthoformate (1.28 ml) and the whole was stirred at room temperature for 2.5 hours. The resultant was added with sodium borohydride (0.441 g) under ice-cooling and stirred at room temperature for 0.5 hours. The reaction solution was concentrated under reduced pressure. The residue was added with water and subjected to extraction with chloroform. The organic

layer was washed with a saturated saline solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (1.71 g) as a brown oily substance.

MS(FAB,Pos.):m/z=486[M+H]$^+$

Example 21-5: Synthesis of (4-{[(4-dipropylamino-butyl)-methanesulfonyl-amino]-methyl}-benzyl)-(1-methyl-1H-imidazol-2-ylmethyl)-carbamic acid t-butyl ester

The compound (182.6 mg) obtained in Example 21-4 was dissolved in dichloromethane (5.3 ml) and added with triethylamine (0.105 ml) and methanesulfonyl chloride (43.6 μl), and the whole was stirred at room temperature for 0.5 hours. The reaction solution was added with water, subjected to extraction with chloroform, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (148.0 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=564[M+H]$^+$

Example 21-6: Synthesis of N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-methanesulfonamide [Compound No. 21]

The compound (148.0 mg) obtained in Example 21-5 was dissolved in methanol (2.9 ml) and added with a 4 mol/l hydrogen

chloride/dioxane solution (2.9 ml) and the whole was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure. The residue was added with a 1 mol/l sodium hydroxide aqueous solution, subjected to extraction with chloroform, dried with anhydrous sodium sulfate, and concentrated under reduced pressure, followed by drying under vacuum.

The resultant was dissolved in methanol (6.09 ml) and added with 2-imidazole carboxaldehyde (43.4 mg) and sodium cyanoborohydride (33.0 mg). The solution was adjusted to pH 5 with acetic acid and stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure. The residue was added with a saturated sodium hydrogen carbonate aqueous solution, subjected to extraction with chloroform, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (102.4 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=544$[M+H]^+$

^{1}H-NMR(500Mz,DMSO-d_6+D_2O):δ=0.89(6H,t,J=7.3Hz),1.43-1.62(8H,m),2.90-3.11(8H,m),2.96(3H,s),3.69(5H,s),4.06(2H,s),4.13(2H,s),4.27(2H,s),7.27(2H,d,J=8.1Hz),7.33(2H,d,J=8.1Hz),7.50(2H,s),7.61(2H,s).

[Example 22]

[0070]

Production example 22: Synthesis of N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(1

-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-4-methyl-benzenesulfonamide [Compound No. 22]

Example 22-1: Synthesis of (4-{[(4-dipropylamino-butyl)-(toluene-4-sulfonyl)-amino]-methyl}-benzyl)-(1-methyl-1H-imidazol-2-ylmethyl)-carbamic acid t-butyl ester

The compound (182.0 mg) obtained in Example 21-4 was dissolved in dichloromethane (5.3 ml) and added with triethylamine (0.104 ml) and p-toluenesulfonyl chloride (107.2 mg), and the whole was stirred at room temperature for 0.5 hours.

The reaction solution was added with water, subjected to extraction with chloroform, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (219 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=640$[M+H]^+$

Example 22-2: Synthesis of N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-4-methyl-benzenesulfonamide [Compound No. 22]

The compound (219.5 mg) obtained in Example 22-1 was dissolved in methanol (4.3 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (4.3 ml) and the whole was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure. The residue was added with a 1 mol/l sodium hydroxide aqueous solution, subjected to extraction with chloroform, dried with anhydrous sodium sulfate,

and concentrated under reduced pressure, followed by drying under vacuum.

The resultant was dissolved in methanol (9.2 ml) and added with 2-imidazole carboxaldehyde (56.7 mg) and sodium cyanoborohydride (43.1 mg). The solution was adjusted to pH 5 with acetic acid and stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure. The residue was added with a saturated sodium hydrogen carbonate aqueous solution, subjected to extraction with chloroform, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (164.4 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=620[M+H]$^+$

^{1}H-NMR(500Mz,DMSO-d_6+D_2O):δ=0.88(6H,t,J=7.3Hz),1.26-1.60(8H,m),2.42(3H,s),2.83-3.06(8H,m),3.63(3H,s),3.69(2H,s),4.05(2H,s),4.13(2H,s),4.23(2H,s),7.21(2H,d,J=8.3Hz),7.31(2H,d,J=8.0Hz),7.46(2H,d,J=8.0Hz),7.50(2H,s),7.61(2H,s),7.75(2H,d,J=8.3Hz).

[Example 23]

[0071]

Production example 23: Synthesis of N-ethyl-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N',N'-dipropyl-butane-1,4-diamine [Compound No. 23]

Example 23-1: Synthesis of 4-(t-butoxycarbonylamino-methyl)-benzoic acid methyl ester

4-aminomethylbenzoic acid methyl ester hydrochloride was subjected to desalting, thereby obtaining a free compound (20.2 g). The free compound was dissolved in anhydrous chloroform (400 ml) and added with triethylamine (34.1 ml) and di-t-butylcarbonate (32.0 g), and the whole was stirred overnight at room temperature under a nitrogen atmosphere. After completion of the reaction, the solvent was distilled off. The resultant was dissolved in chloroform and added with distilled water, and the whole was stirred for a while. The resultant was subjected to extraction with chloroform and washed with a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (35.7 g) as a colorless crystal.

MS(FAB,Pos.):m/z=266$[M+H]^+$

Example 23-2: Synthesis of (4-hydroxymethyl-benzyl)-carbamic acid t-butyl ester

The compound (35.7 g) obtained in Example 23-1 was dissolved in anhydrous THF (800 ml) and added with Lithium aluminum hydride (10.2 g) in an ice bath and the whole was stirred for 2 days under a nitrogen atmosphere. After completion of the reaction, methanol and then an aqueous sodium potassium tartrate solution were added thereto and the whole was stirred overnight. The resultant was subjected to extraction with chloroform and washed with saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (29.2 g) as a colorless crystal.

[0072]

Example 23-3: Synthesis of (4-formyl-benzyl)-carbamic acid t-butyl ester

The compound (17.6 g) obtained in Example 23-2 was dissolved in chloroform (400 ml) and then added with manganese dioxide (chemically processed product) (88.2 g) and the whole was stirred overnight at room temperature. After completion of the reaction, the resultant was filtrated through Celite. The solvent was distilled off, thereby obtaining the subject compound (20.4 g) as a colorless crystal.

[0073]

Example 23-4: Synthesis of {4-[(4-dipropylamino-butylamino)-methyl]-benzyl}-carbamic acid t-butyl ester

The compound (9.25 g) obtained in Example 1-2 was dissolved in anhydrous methanol (200 ml) and then added with trimethyl orthoformate (8.81 ml) and the compound (12.6 g) obtained in Example 23-3. The whole was stirred at room temperature for 1.5 hours under a nitrogen atmosphere. Then, sodium borohydride (2.03 g) was added thereto in an ice bath and the whole was stirred at room temperature for 2 hours. After completion of the reaction, distilled water was added thereto and the whole was stirred for a while. The solution was subjected to extraction with chloroform and washed with a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (19.3 g) as a colorless oily substance.

[0074]

Example 23-5: Synthesis of (4-{[(4-dipropylamino-butyl)-ethyl-amino]-methyl}-benzyl)-carbamic acid t-butyl ester

The compound (289 mg) obtained in Example 23-4 was dissolved in anhydrous methanol (6.0 ml) and added with sodium cyanoborohydride (92.8 mg), acetic acid (1.00 ml), and acetaldehyde (61.3 μl). The whole was stirred overnight at room temperature under a nitrogen atmosphere. After completion of the reaction, the solvent was distilled off. The resultant was dissolved in chloroform and added with a 1 mol/l sodium hydroxide aqueous solution, followed by stirring for a while. The resultant was subjected to extraction with chloroform, washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (311 mg) as a pale-yellow oily substance.

[0075]

Example 23-6: Synthesis of N-(4-aminomethyl-benzyl)-N-ethyl-N',N'-dipropyl-butane-1,4-diamine

The compound (311 mg) obtained in Example 23-5 was dissolved in anhydrous methanol (1.0 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (3.0 ml) and the whole was stirred at room temperature for 1 hour. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution, subjected to extraction with chloroform, and washed with a saturated saline solution.

The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (219 mg) as a pale-yellow oily substance.

MS(FAB,Pos.):m/z=320$[M+H]^+$

Example 23-7: Synthesis of N-ethyl-N-(4-{[(1H-imidazol-2-ylmethyl)amino]methyl}benzyl)-N',N'-dipropyl-butane-1,4-diamine

The compound (219 mg) obtained in Example 23-6 was dissolved in anhydrous methanol (5.0 ml) and added with trimethyl orthoformate (112 μl) and 2-imidazole carboxaldehyde (72.4 mg) and the whole was stirred overnight at room temperature under a nitrogen atmosphere. Subsequently, sodium borohydride (12.3 mg) was added thereto in an ice bath, and the whole was stirred at room temperature for 1 hour. After completion of the reaction, distilled water was added thereto and the whole was stirred for a while. The resultant was subjected to extraction with chloroform and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution. The organic layer obtained was dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (317 mg) as a yellow oily substance.

[0076]

Example 23-8: Synthesis of N-ethyl-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N',N'-dipropyl-butane-1,4-diamine [Compound No. 23]

The compound (317 mg) obtained in Example 23-7 was dissolved

in anhydrous methanol (6.0 ml) and added with sodium cyanoborohydride (74.8 mg), acetic acid (1.00 ml), and 1-methyl-2-imidazole carboxaldehyde (105 mg) and the whole was stirred overnight at room temperature under a nitrogen atmosphere. After completion of the reaction, the solvent was distilled off and the resultant was dissolved in chloroform and added with a 1 mol/l sodium hydroxide aqueous solution. The whole was stirred for a while and subjected to extraction with chloroform, followed by washing with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution. The organic layer obtained was dried with anhydrous sodium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (318 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=494$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6+D_2O):δ=0.92(6H,t,J=7.2Hz),1.24(3H,t,J=7.3Hz),1.62-1.68(6H,m),1.76-1.78(2H,m),2.92-3.02(4H,m),3.05-3.08(2H,m),3.62(2H,s),3.69(2H,s),3.71(3H,s),3.74(2H,s),4.10(2H,s),4.17(2H,s),4.17-4.19(1H,m),4.26-4.29(1H,m),7.41(2H,d,J=7.9Hz),7.48(2H,d,J=8.7Hz),7.49(2H,s),7.61(2H,s).

[Example 24]

[0077]

Production example 24: Synthesis of N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N-phenyl-N',N'-dipropyl-butane-1,4-diamine [Compound No. 24]

Example 24-1: Synthesis of

N'-phenyl-N,N-dipropyl-butane-1,4-diamine

The compound (357.7 mg) obtained in Example 17-5 was dissolved in anhydrous methanol (14 ml) and added with aniline (0.209 ml) and trimethyl orthoformate (0.686 ml) and the whole was stirred at room temperature for 3 hours. Sodium borohydride (237.2 mg) was added thereto and the whole was stirred at room temperature for 1 hour. After completion of the reaction, the solvent was distilled off. The resultant was added with water, subjected to extraction with chloroform, and dried with magnesium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (165.2 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=249$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.87(6H,t,J=7.3Hz),1.41-1.49(4H,m),1.52-1.58(2H,m),1.63(2H,quint.,J=7.1Hz),2.35-2.39(4H,m),2.44(2H,t,J=7.1Hz),3.12(2H,t,J=6.8Hz),6.60(2H,dd,J=1.0,8.5Hz),6.68(1H,t,J=7.3Hz),7.17(2H,t,J=7.3Hz).

Example 24-2: Synthesis of 4-{[(4-dipropylamino-butyl)-phenyl-amino]-methyl}-benzonitrile

The compound (152.5 mg) obtained in Example 24-1 was dissolved in anhydrous DMF (6.1 ml) and added with cesium carbonate (299.0 mg) and 4-bromomethyl-benzonitrile (manufactured by Tokyo Kasei Kogyo Co., Ltd.) (184.0 mg). The whole was stirred overnight at 60°C and then stirred at 80°C for additional 24 hours. After completion of the reaction, the solvent was distilled off. The resultant was added with water, subjected to extraction with

chloroform, and dried with magnesium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (88.8 mg) as a colorless oily substance.
MS(FAB,Pos.):m/z=363[M+H]$^+$

Example 24-3: Synthesis of
N-(4-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N-phenyl-N',N'-dipropyl-butane-1,4-diamine

The compound (88.8 mg) obtained in Example 24-2 was dissolved in anhydrous THF (3.5 ml) and added with Lithium aluminum hydride (36.4 mg). The whole was stirred at room temperature for 4 hours and then stirred at 60°C for additional 2 hours. After completion of the reaction, ethyl acetate was added thereto. The resultant was added with an aqueous sodium potassium tartrate solution and stirred, followed by extraction with chloroform. The resultant was dried with magnesium sulfate and the solvent was distilled off under reduced pressure.

The resultant was dissolved in anhydrous methanol (3.5 ml) and added with 2-imidazole carboxaldehyde (34.6 mg) and trimethyl orthoformate (0.079 ml) and the whole was stirred at room temperature for 13 hours. The resultant was added with sodium borohydride (27.2 mg) and stirred at room temperature for 2 hours. The resultant was added with water, subjected to extraction with chloroform, and dried with magnesium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (45.5 mg) as a colorless oily substance.
MS(FAB,Pos.):m/z=448[M+H]$^+$

Example 24-4: Synthesis of N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N-phenyl-N',N'-dipropyl-butane-1,4-diamine [Compound No. 24]

The compound (45.5 mg) obtained in Example 24-3 was dissolved in anhydrous methanol (1.8 ml) and added with 1-methyl-2-imidazole carboxaldehyde (16.5 mg) and sodium cyanoborohydride (18.9 mg). The solution was adjusted to pH 5 with acetic acid and stirred at room temperature for 24 hours. After completion of the reaction, the solvent was distilled off and the resultant was added with a 1 mol/l sodium hydroxide aqueous solution and subjected to extraction with chloroform. The resultant was dried with magnesium sulfate and the solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (32.7 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=542$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6+D_2O):δ=0.90(6H,t,J=7.1Hz),1.60-1.67(8H,m),2.96-2.99(4H,m),3.04-3.07(2H,m),3.43(2H,t,J=7.1Hz),4.03(2H,s),4.11(2H,s),4.49(2H,s),6.66(3H,br),7.10(2H,d,J=7.9Hz),7.15(2H,t,J=7.9Hz),7.23(2H,d,J=7.9Hz),7.45(2H,s),7.58(2H,s).

[Example 25]

[0078]

Production example 25: Synthesis of N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-aceta

mide [Compound No. 25]

Example 25-1: Synthesis of (4-{[(4-dipropylamino-butyl)-acetamino]-methyl}-benzyl)-(1-methyl-1H-imidazol-2-ylmethyl)-carbamic acid t-butyl ester

The compound (182.6 mg) obtained in Example 21-4 was dissolved in chloroform (7.0 ml) and added with triethylamine (0.133 ml) and acetic anhydride (73.5 mg) and the whole was stirred at room temperature for 24 hours. The reaction solution was added with water, subjected to extraction with chloroform, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (253.2 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=528$[M+H]^+$

Example 25-2: Synthesis of N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-acetamide [Compound No. 25]

The compound (237.9 mg) obtained in Example 25-1 was dissolved in methanol (4.7 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (4.7 ml) and the whole was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure. The residue was added with a 1 mol/l sodium hydroxide aqueous solution, subjected to extraction with chloroform, dried with anhydrous sodium sulfate, and concentrated under reduced pressure, followed by drying under vacuum.

The resultant was dissolved in methanol (9.6 ml) and added

with 2-imidazole carboxaldehyde (74.5 mg) and sodium cyanoborohydride (56.7 mg). The solution was adjusted to pH 5 with acetic acid and stirred at room temperature for 20 hours. The reaction solution was concentrated under reduced pressure . The residue was added with a saturated sodium hydrogen carbonate aqueous solution, subjected to extraction with chloroform, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (186.1 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=508[M+H]$^+$

^{1}H-NMR(500Mz,DMSO-d_6+D_2O):δ=0.90(6H,t,J=7.3Hz),1.49-1.67(8H,m),2.00(3H,s),2.95-3.04(6H,m),3.17-3.24(2H,m),3.67(3H,s),3.70(2H,s),4.07(2H,m),4.15(2H,m),4.43(2H,s),4.49(2H,s),7.08(1H,d,J=8.1Hz),7.11(1H,d,J=8.1Hz),7.29(1H,d,J=8.1Hz),7.34(1H,d,J=8.1Hz),7.49(2H,s),7.60(2H,s).

[Example 26]

[0079]

Production example 26: Synthesis of 1-(4-dipropylamino-butyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-1-methyl-urea [Compound No. 26]

Example 26-1: Synthesis of 3-(4-cyano-phenyl)-1-(4-dipropylamino-butyl)-1-methyl-urea

Acetic anhydride (1.23 ml) was cooled with ice and then added with formic acid (0.604 ml) and the whole was stirred at 50°C for 2 hours. After completion of the reaction, the solution

was left standing for cooling and anhydrous THF (1.0 ml) was added thereto. The whole was cooled with ice and a THF solution (2.0 ml) containing the compound (896.0 mg) obtained in Example 1-2 was added thereto, followed by stirring at room temperature for 30 minutes. After completion of the reaction, the solvent was distilled off.

The resultant was dissolved in anhydrous THF (30 ml) and added with Lithium aluminum hydride (592 mg) and the whole was stirred at room temperature for 1 hour and then refluxed under heating for 2 hours. After ethyl acetate was added thereto, the resultant was added with an aqueous sodium potassium tartrate solution and was stirred at room temperature, followed by extraction with chloroform. The resultant was dried with magnesium sulfate and the solvent was distilled off.

The resultant was dissolved in toluene (30 ml) and added with 4-isocyanat-benzonitrile (manufactured by Aldrich Corporation) (910.9 mg) and the whole was stirred at room temperature for 14 hours. After completion of the reaction, the solvent was distilled off. The residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (97.6 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=331$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.3Hz),1.41-1.53(6H,m),1.61-1.68(4H,m),2.36-2.40(4H,m),2.45(2H,t,J=7.1Hz),3.03(3H,s),3.36(2H,t,J=7.6Hz),6.78(1H,br),7.50-7.53(2H,m),7.55-7.57(2H,m).

Example 26-2: Synthesis of

1-(4-dipropylamino-butyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-1-methyl-urea [Compound No. 26]

The compound (97.6 mg) obtained in Example 26-1 was dissolved in ethanol (4.0 ml), and a 1 mol/l sodium hydroxide aqueous solution (1.0 ml) and Raney nickel (10 mg) were added thereto. The whole was stirred at room temperature for 16 hours under a hydrogen atmosphere. After completion of the reaction, the resultant was subjected to filtration through Celite. The filtrate was added with water, subjected to extraction with chloroform, and dried with magnesium sulfate, thereby distilling the solvent off under reduced pressure.

[0080]

The resultant was dissolved in methanol (3.4 ml) and added with 2-imidazole carboxaldehyde (36.5 mg) and trimethyl orthoformate (0.082 ml), followed by stirring at room temperature for 16.5 hours. The resultant was added with sodium borohydride (28.4 mg) and the whole was stirred at room temperature for 3 hours. After completion of the reaction, the solvent was distilled off. The resultant was added with water, subjected to extraction with chloroform, and dried with magnesium sulfate. The solvent was distilled off.

[0081]

The resultant was dissolved in methanol (4.0 ml) and added with 1-methyl-2-imidazole carboxaldehyde (39.6 mg) and sodium cyanoborohydride (45.2 mg). The solution was adjusted to pH 5 with acetic acid and stirred at room temperature for 22 hours. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous

solution, subjected to extraction with chloroform, and dried with magnesium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (76.8 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=509[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.88(6H,t,J=7.3Hz),1.51-1.55(2H,m),1.60-1.70(6H,m),2.92-2.96(4H,m),2.94(3H,s),3.03-3.06(2H,m),3.32(2H,t,J=7.2Hz),3.58(2H,s),3.69(3H,s),4.04(2H,s),4.11(2H,s),7.25(2H,d,J=8.7Hz),7.42(2H,d,J=8.5Hz),7.56(2H,dd,J=2.0,7.1Hz),7.64(2H,s),8.30(1H,s)10.24(1H,s),14.79(2H,br).

[Example 27]

[0082]

Production example 27: Synthesis of 1-(4-dipropylamino-butyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-1,3-dimethyl-urea [Compound No. 27]

Example 27-1: Synthesis of 1-(4-cyano-phenyl)-3-(4-dipropyl-butyl)-1,3-dimethyl-urea

The compound (197.3 mg) obtained in Example 26-1 was dissolved in anhydrous THF (6.0 ml) and added with 60% sodium hydride (27.5 mg) and the whole was stirred at room temperature for 1.5 hours. The resultant was added with methyl iodide (0.045 ml) and stirred at room temperature for 2 hours. After completion of the reaction, the solvent was distilled off. The resultant was added with water, subjected to extraction with chloroform, and dried with magnesium sulfate. The solvent was distilled off.

The residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (37.8 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=345[M+H]$^+$

Example 27-2: Synthesis of 1-(4-dipropylamino-butyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amine]-methyl}-phenyl)-1,3-dimethyl-urea [Compound No. 27]

The compound (37.8 mg) obtained in Example 27-1 was dissolved in ethanol (1.5 ml), and a 1 mol/l sodium hydroxide aqueous solution (0.4 ml) and Raney nickel (3.8 mg) were added thereto. The whole was stirred at room temperature for 4 hours under a hydrogen atmosphere. After completion of the reaction, the resultant was subjected to filtration through Celite. The solvent was distilled off. Then the resultant was subjected to extraction with chloroform, and the solvent was distilled off.

The resultant was dissolved in methanol (1.2 ml) and added with 2-imidazole carboxaldehyde (12.9 mg) and trimethyl orthoformate (0.029 ml), followed by stirring at room temperature for 3 days. The resultant was added with sodium borohydride (10.1 mg) and the whole was stirred at room temperature for 4 hours. After completion of the reaction, the solvent was distilled off. The resultant was added with water, subjected to extraction with chloroform, and dried with magnesium sulfate. The solvent was distilled off.

The resultant was dissolved in methanol (1.6 ml) and added with 1-methyl-2-imidazole carboxaldehyde (14.8 mg) and sodium cyanoborohydride (16.8 mg). The solution was adjusted to pH 5

with acetic acid and stirred overnight at room temperature. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution, subjected to extraction with chloroform, and dried with magnesium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (39.5 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=523$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.90(6H,t,J=7.3Hz),1.43-1.48(2H,m),1.54-1.57(2H,m),1.63-1.71(4H,m),2.47(3H,s),2.89-3.06(6H,m),3.00(3H,s),3.11(2H,t,J=7.3Hz),3.65(3H,s),3.70(3H,s),4.11(2H,s),4.19(2H,s),7.06(2H,d,J=8.4Hz),7.35(2H,d,J=8.5Hz),7.53(2H,dd,J=2.0,6.8Hz),7.63(2H,s),10.45(1H,br),14.80(1H,br),14.92(1H,br).

[Example 28]

[0083]

Production example 28: Synthesis of N-methyl-N-[4-({(1-methyl-1H-imidazol-2-ylmethyl)-[1-(toluene-4-sulfonyl)-1H-imidazol-2-ylmethyl]-amino}-methyl)-benzyl]-N",N"-dipropyl-butane-1,4-diamine [Compound No. 28]

Example 28-1: Synthesis of N-methyl-N",N"-dipropyl-N-[4-({[1-(toluene-4-sulfonyl)-1H-imidazol-2-ylmethyl]-amino}-methyl)-benzyl]-butane-1,4-diamine

The compound (568 mg) obtained in Example 9-2 was dissolved in anhydrous THF (11 ml) and the whole was added 60% sodium hydride (157 mg) while being stirred under ice-cooling under a nitrogen

atmosphere. The whole was then warmed back to room temperature and stirred for 1 hour. Under ice-cooling, a THF solution (2.0 ml) containing p-toluenesulfonyl chloride (315 mg) was gradually dropped therein and the whole was stirred for 30 minutes while being kept under ice-cooling. After completion of the reaction, acetic acid (220 μl) was added to neutralize the resultant while the whole was stirred under ice-cooling, and water was added thereto to stop the reaction. The resultant was warmed back to room temperature. The solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and added with a 1 mol/l sodium hydroxide aqueous solution to make the pH of the aqueous layer about 10. The aqueous layer was extracted with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the resultant was concentrated and evaporated to dryness under reduced pressure, thereby obtaining the subject compound (678 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=540$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=6.3Hz),1.42-1.52(8H,m),2.16(3H,s),2.18-2.41(8H,m),2.42(3H,s),3.46(2H,s),3.76(2H,s),4.03(2H,s),6.98(1H,d,J=1.7Hz),7.22(1H,dd,J=2.0,6.3Hz),7.25(1H,dd,J=2.0,4.2Hz),7.29(2H,dd,J=0.7,2.0Hz),7.30(2H,dd,J=0.7,2.0Hz),7.42(1H,d,J=1.7Hz),7.76(1H,dd,J=2.0,2.0Hz),7.79(1H,dd,J=2.0,2.0Hz).

Example 28-2: Synthesis of N-methyl-N-[4-({(1-methyl-1H-imidazol-2-ylmethyl)-[1-(toluene-4-sulfonyl)-1H-imidazol-2-ylmethyl]-amino}-methyl)-benzyl]-N",N"-dipropyl-butane-1,4-diamine [Compound No. 28]

The compound (307 mg) obtained in Example 28-1 was dissolved in anhydrous DMF (6.0 ml), added with potassium carbonate (175 mg) at room temperature under a nitrogen atmosphere, and added with the compound (107 mg) obtained in Example 10-2 under ice-cooling. The whole was stirred at room temperature for 2 hours and stirred at 60°C for additional 22 hours. The resultant was left standing for cooing and then added with water under ice-cooling to stop the reaction. The solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and added with water. The aqueous layer was extracted with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate.

After filtration, the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (49.3 mg) as a brown oily substance.

MS(FAB,Pos.):m/z=634[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.3Hz),1.41-1.51(8H,m),2.15(3H,s),2.33-2.39(8H,m),2.41(3H,s),3.43(3H,s),3.45(2H,s),3.70(2H,s),3.71(2H,s),3.85(2H,s),6.79(1H,d,J=1.2Hz),6.92(1H,d,J=1.2Hz),6.98(1H,d,J=1.7Hz),7.23(1H,dd,J=7.0,8.2Hz),7.26(1H,dd,J=0.6,2.9Hz),7.27(2H,dd,J=0.6,0.6Hz),7.27(2H,dd,J=0.6,4.1Hz),7.40(1H,d,J=1.7Hz),7.57(1H,dd,J=1.8,2.0Hz),7.79(1H,dd,J=1.7,2.0Hz).

[Example 29]

[0084]

Production example 29: Synthesis of

[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylm

ethyl)-amino]-methyl}-1-methyl-1H-benzimidazol-2-yl)-benzyl]-dipropyl-amine [Compound No. 29]

Example 29-1: Synthesis of 3,4-diaminobenzonitrile

3-Nitro-4-aminobenzonitrile (3.00 g) was dissolved in ethanol (300 ml) and added with stannous chloride dihydrate (20.7 g) and the whole was heated to 60°C. Sodium borohydride (348 mg) was gradually added thereto and the whole was stirred overnight at 60°C. After completion of the reaction, the resultant was added with water (300 ml) and neutralized with a 5 mol/l sodium hydroxide aqueous solution. After ethanol was distilled off under reduced pressure, the aqueous layer was added with ethyl acetate for extraction. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was recrystallized, thereby obtaining the subject compound (1.11 g) as a brown crystal.

MS(EI):m/z=133$[M]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=6.68(1H,d,J=8.1Hz),6.95(1H,s),7.05(1H,d,J=8.1Hz).

Example 29-2: Synthesis of 4-dipropylaminomethyl-benzoic acid methyl ester

4-Bromomethylbenzoic acid methyl ester (831 mg) was dissolved in DMF (12.5 ml) and added with dipropylamine (971 µl) and the whole was stirred at room temperature for 2 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform, washed with a saturated aqueous sodium hydrogen carbonate solution, and subjected to extraction with chloroform. The organic layer

was washed with a saturated saline solution and dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off, thereby obtaining the subject compound (883 mg) as a brown solid.

[0085]

Example 29-3: Synthesis of 4-dipropylaminomethyl-benzoic acid

The compound (883 mg) obtained in Example 29-2 was dissolved in methanol (18 ml) and added with a 1 mol/l sodium hydroxide aqueous solution (9.0 ml) and the whole was stirred overnight at room temperature. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in 1 mol/l hydrochloric acid, subjected to extraction with chloroform, and dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off and the residue was dried under vacuum, thereby obtaining the subject compound (820 mg) as a white solid.

MS(FAB,Pos.):m/z=236$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.86(6H,t,J=7.3Hz),1.74(4H,sext.,J=7.3Hz),2.92(4H,br),4.38(2H,d,J=4.6Hz),7.78(2H,d,J=8.0Hz),8.00(1H,d,J=8.0Hz),10.85(1H,br).

Example 29-4: Synthesis of
N-(2-amino-5-cyano-phenyl)-4-dipropylaminomethyl-benzamide

The compound (1.01 g) obtained in Example 29-3, WSCI hydrochloride (973 mg), and HOBt (894 mg) were dissolved in chloroform (30 ml), and the whole was stirred for 2 hours. Then, the compound (445 mg) obtained in Example 29-1 was added thereto and the whole was stirred at room temperature for 3 hours. After

completion of the reaction, the solvent was distilled off under reduced pressure. Then, the residue was dissolved in chloroform and washed with a saturated ammonium chloride aqueous solution, a saturated aqueous sodium hydrogen carbonate solution, and a saturated saline solution. After that, the resultant was dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (613 mg) as an orange solid.

MS(FAB,Pos.):m/z=351$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.87(6H,t,J=7.3Hz),1.48(4H,sext.,J=7.3Hz),2.38(4H,t,J=7.3Hz),3.62(2H,s),4.43(3H,br),6.83(1H,d,J=8.3Hz),7.37(1H,d,J=8.3Hz),7.49(2H,d,J=8.1Hz),7.52(1H,s),7.80(1H,br),7.84(1H,d,J=8.1Hz).

Example 29-5: Synthesis of 2-(4-dipropylaminomethyl-phenyl)-3-methyl-3H-benzimidazol-5-carbonitrile

The compound (613 mg) obtained in Example 29-4 was dissolved in THF (18 ml) and added with 60% sodium hydride (105 mg). After that, the whole was gradually added with methyl iodide (373 mg) and stirred at room temperature for 16 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform, washed with water, and subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off. The residue was purified through silica gel column

chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (160 mg) as a brown solid.

MS(FAB,Pos.):m/z=347[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.88(6H,t,J=7.3Hz),1.50(4H,sext.,J=7.3Hz),2.41(4H,t,J=7.3Hz),3.64(2H,s),3.93(3H,s),7.55(2H,d,J=8.3Hz),7.57(1H,d,J=8.3Hz),7.72(2H,d,J=8.3Hz),7.74(1H,s),7.86(1H,d,J=8.3Hz).

Example 29-6: Synthesis of [4-(6-aminomethyl-1-methyl-1H-benzimidazol-2-yl)-benzyl]-dipropyl-amine

Lithium aluminum hydride (64.0 mg) was suspended in THF (5.0 ml) and the whole was cooled to 0°C. A THF solution (5.0 ml) containing the compound (155 mg) obtained in Example 29-5 was dropped therein and the whole was stirred at 0°C for 1 hour. After completion of the reaction, sodium sulfate decahydrate was added thereto until bubbling was stopped, and a 1 mol/l sodium hydroxide aqueous solution was then added thereto until a white precipitate was generated. A solid was separated by filtration and the solvent in the filtrate was then distillated off under reduced pressure, and the residue was dried under vacuum, thereby obtaining the subject compound (93.5 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=351[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.94(6H,t,J=7.3Hz),1.71-1.89(4H,m),2.98(2H,s),3.13-3.20(2H,m),3.23-3.30(2H,m),3.99(3H,s),4.64(2H,s),7.67(1H,d,J=8.3Hz),7.78(2H,d,J=8.3Hz),7.87(1H,d,J=8.3Hz),8.05(2H,d,J=8.3Hz),8.35(1H,s).

Example 29-7: Synthesis of [4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-methyl-1H-benzimidazol-2-yl)-benzyl]-dipropyl-amine [Compound No. 29]

The compound (93.5 mg) obtained in Example 29-6 was dissolved in methanol (4.0 ml) and added with trimethyl orthoformate (100 µl) and 2-imidazole carboxaldehyde (31.7 mg) and the whole was stirred at room temperature for 1 hour. After having been cooled to 0°C, the solution was added with sodium borohydride (13.2 mg). The whole was warmed back to room temperature and stirred for 30 minutes.

After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform, washed with a saturated aqueous sodium hydrogen carbonate solution, and subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure.

The resultant was dissolved in methanol (4.0 ml) and added with acetic acid (100 µl) and 1-methyl-2-imidazole carboxaldehyde (61.0 mg), followed by stirring at room temperature for 30 minutes. The resultant was added with sodium cyanoborohydride (53.6 mg) and the whole was stirred at room temperature for 3 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform, washed with a saturated aqueous sodium hydrogen carbonate solution, and subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried anhydrous with sodium sulfate. After filtration, the solvent was distilled

off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (38.4 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=525[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.89(6H,t,J=7.3Hz),1.72-1.82(4H,m),2.94-3.02(4H,m),3.75(3H,s),3.94(2H,s),4.13(3H,s),4.16(2H,s),4.24(2H,s),4.48(2H,d,J=5.6Hz),7.53-7.54(2H,m),7.59(1H,d,J=8.5Hz),7.64(2H,s),7.75(1H,d,J=8.5Hz),8.04(2H,d,J=8.7Hz),8.07(2H,d,J=8.7Hz),8.33(1H,s).

[Example 30]

[0086]

Production example 30: Synthesis of 6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-imidazo[1,2-a]pyridine-2-carboxylic acid-(4-dipropyl)-amino-butyl)-amide [Compound No. 30]

Example 30-1: Synthesis of 6-amino-pyridine-3-carboxaldehyde

2-Amino-5-cyanopyridine (1.02 g) was dissolved in THF (40 ml) and added with Lithium aluminum hydride (637 mg) and the whole was stirred at room temperature for 2 hours. Water was added thereto to stop the reaction, and the whole was added with a saturated sodium sulfate aqueous solution and subjected to filtration through Celite. The residue obtained by concentration of the filtrate was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (1.04 g) as a yellow solid.

MS(EI):m/z=122[M]$^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=6.51(1H,dd,J=0.7,8.9Hz),7.19(2H,br),

7.75(1H,dd,J=2.4,8.9Hz),8.43(1H,dd,J=0.5,2.2Hz),9.66(1H,s).

Example 30-2: Synthesis of
6-formyl-imidazo[1,2-a]pyridine-2-carboxylic acid ethyl ester

An ethanol solution (8.0 ml) containing the compound (318 mg) obtained in Example 30-1 was added with 3-bromo-2-oxo-propionic acid ethyl ester (0.33 ml) and the whole was stirred at room temperature for 18 hours. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (230 mg) as a yellow solid.

MS(FAB,Pos.):m/z=219$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=1.46(3H,t,J=7.0Hz),4.49(2H,q,J=7.0Hz),
7.73-7.79(2H,m),8.33(1H,d,J=0.5Hz),8.72(1H,dd,J=1.0,1.7Hz),9
.99(1H,s).

Example 30-3: Synthesis of
6-{[(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-imidazo
[1,2-a]pyridine-2-carboxylic
acid-(4-dipropylamino-butyl)-amide

A 15% trimethyl aluminum/hexane solution (0.32 ml) was dropped into a dichloromethane solution (2.0 ml) containing the compound (72.0 mg) obtained in Example 1-2 and the whole was stirred at room temperature for 15 minutes. A dichloromethane solution (2.0 ml) containing the compound (41.8 mg) obtained in Example 30-2 was dropped thereto and the whole was stirred at room temperature for 20 hours. To this solution, 1 mol/l hydrochloric acid was dropped to stop the reaction, and the whole was neutralized with a saturated aqueous sodium hydrogen carbonate solution and

then subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution and dried with anhydrous sodium sulfate.

Of the resultant residue (65.2 mg), 40.2 mg thereof was dissolved in methanol (2.0 ml) and added with trimethyl orthoformate (0.040 ml). A methanol solution (1.0 ml) containing the compound (20.0 mg) obtained in Example 14-7 was dropped thereto and the whole was stirred at room temperature for 4 hours. After having been cooled to 0°C, the resultant was added with sodium borohydride (6.8 mg), warmed to room temperature, and stirred for 30 minutes. Water was added thereto to stop the reaction and the concentrated residue was extracted with chloroform. The organic layer was washed with water and a saturated saline solution and dried with anhydrous sodium sulfate.

The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (34.7 mg) as a pale-yellow oily substance.

MS(FAB,Pos.):m/z=440$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.3Hz),1.43-1.48(4H,m),1.55-1.57(2H,m),1.63-1.66(2H,m),2.37(4H,t,J=7.3Hz),2.46(2H,br),3.48(2H,tt,J=6.3,6.9Hz),3.64(3H,s),3.85(2H,s),3.89(2H,s),6.82(1H,d,J=1.2Hz),6.94(1H,d,J=1.2Hz),7.26(1H,dd,J=1.7,9.3Hz),7.41(1H,t,J=5.8Hz),7.50(1H,d,J=9.3Hz),8.08(1H,d,J=0.6Hz),8.10(1H,d,J=1.1Hz).

Example 30-4: Synthesis of

6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethy

1)-amino]-methyl}-imidazo[1,2-a]pyridine-2-carboxylic acid-(4-dipropyl)-amino-butyl)-amide [Compound No. 30]

The compound (34.7 mg) obtained in Example 30-3 was dissolved in methanol (3.0 ml) and added with 2-imidazole carboxaldehyde (9.1 mg) and sodium cyanoborohydride (9.9 mg). The solution was adjusted to pH 4 with acetic acid and stirred at room temperature for 45 hours. A saturated aqueous sodium hydrogen carbonate solution was added thereto to stop the reaction and the whole was subjected to extraction with chloroform. The organic layer was washed with water and a saturated saline solution and dried with anhydrous sodium sulfate. The residue obtained by distilling the solvent off was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (23.6 mg) of the subject compound as a pale-yellow solid.

MS(FAB,Pos.):m/z=520$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.3Hz),1.26-1.48(4H,m),1.51-1.56(2H,m),1.61-1.67(2H,m),2.34-2.37(4H,m),2.44(2H,t,J=7.3Hz),3.48(2H,tt,J=6.4,6.9Hz),3.56(2H,s),3.57(2H,s),3.65(3H,s),3.66(2H,s),6.92(1H,d,J=1.2Hz),7.03(1H,d,J=1.2Hz),7.08(1H,s),7.14(1H,s),7.39(1H,br),7.39(1H,dd,J=1.5,9.5Hz),7.54(1H,d,J=9.3Hz),8.11(1H,d,J=0.7Hz),8.23(1H,d,J=0.7Hz),12.41(1H,br).

[Example 31]

[0087]

Production example 31: Synthesis of N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N',N'-dipropyl-N-(2,2,2-trifluoro-ethyl)-butane-1,4-diamine [Compound No. 31]

Example 31-1: Synthesis of (4-{[(4-dipropylaminobutyl)-(2,2,2-trifluoroacetyl)-amino]-methyl}-benzyl)-(1-methyl-1H-imidazol-2-ylmethyl)-carbamic acid t-butyl ester

The compound (222 mg) obtained in Example 21-4 was dissolved in anhydrous dichloromethane (4.4 ml) and added with triethylamine (0.071 ml). The whole was cooled with ice and added with trifluoroacetic anhydride (0.072 ml), followed by stirring at room temperature for 1.5 hours. After completion of the reaction, the resultant was washed with water and dried with magnesium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (178.6 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=582$[M+H]^+$

Example 31-2: Synthesis of N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N',N'-dipropyl-N-(2,2,2-trifluoro-ethyl)-butane-1,4-diamine [Compound No. 31]

The compound (178.6 mg) obtained in Example 31-1 was dissolved in anhydrous THF (0.9 ml) and added with a 1 mol/l borane-THF complex/THF solution (1.72 ml). The whole was refluxed under heating for 18.5 hours. After completion of the reaction, methanol was added thereto and the solvent was distilled off. The resultant was added with 1 mol/l hydrochloric acid and the whole was refluxed under heating for 3 hours. The solution was neutralized with a 1 mol/l sodium hydroxide aqueous solution and subjected to extraction with chloroform. The resultant was

dried with magnesium sulfate and the solvent was distilled off.

The resultant was dissolved in anhydrous methanol (5.2 ml) and added with 2-imidazole carboxaldehyde (40.4 mg) and sodium cyanoborohydride (52.8 mg). The solution was adjusted to pH 5 with acetic acid and stirred at room temperature for 18 hours. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution, subjected to extraction with chloroform, and dried with magnesium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with acetic acid, thereby obtaining a hydrochloride (138.7 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=548[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6+D_2O):δ=0.90(6H,t,J=7.3Hz),1.47-1.48(2H,m),1.57-1.64(6H,m),2.94-3.00(6H,m),3.21-3.23(2H,m),3.69(6H,s),3.74(3H,s),4.06(2H,s),4.14(2H,s),7.20(2H,d,J=8.1Hz),7.28(2H,d,J=8.1Hz),7.48(2H,s),7.59(2H,s).

[Example 32]

[0088]

Production example 32: Synthesis of N-(4-{[(1-methanesulfonyl-1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N-methyl-N",N"-dipropyl-butane-1,4-diamine [Compound No. 32]

Example 32-1: Synthesis of N-[4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl]-N-methyl-N",N"-dipropyl-butane-1,4-diamine

The compound (26.7 mg) obtained in Example 9-2 was dissolved in anhydrous THF (0.35 ml) and added with triethylamine (350 μl) and a THF solution (50 μl) containing 1-methyl-2-imidazole carboxaldehyde (9.20 mg). The solution was added with sodium triacetoxyborohydride (31.3 mg) and the whole was stirred at room temperature for 24 hours under a nitrogen atmosphere. After completion of the reaction, water was added thereto and the solvent was distilled off under reduced pressure. The residue was added with chloroform and a 1 mol/l sodium hydroxide aqueous solution to make the pH of the aqueous layer 10, and the aqueous layer was extracted with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. After filtration, the resultant was concentrated and evaporated to dryness under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (23.1 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=480$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.3Hz),1.41-1.52(8H,m),2.16(3H,s),2.36-2.44(8H,m),3.46(2H,s),3.55(5H,s),3.62(2H,s),3.67(2H,s),6.87(1H,d,J=1.2Hz),6.99(1H,d,J=1.2Hz),7.10(2H,s),7.27(2H,d,J=8.0Hz),7.35(1H,d,J=8.0Hz).

Example 32-2: Synthesis of N-(4-{[(1-methanesulfonyl-1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N-methyl-N",N"-dipropyl-butane-1,4-diamine [Compound No. 32]

The compound (125 mg) obtained in Example 32-1 was dissolved in anhydrous chloroform, added with triethylamine (60 μl) at room

temperature under a nitrogen atmosphere, and added with methanesulfonyl chloride (25 μl) and the whole was stirred. After completion of the reaction, water and methanol were added thereto to stop the reaction. Water was added thereto and the aqueous layer was extracted with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. After filtration, the resultant was concentrated and evaporated to dryness under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (87.7 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=558$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.3Hz),1.32-1.51(8H,m),2.15(3H,s),2.33-2.41(8H,m),3.39(3H,s),3.44(2H,s),3.45(3H,s),3.76(2H,s),3.89(2H,s),4.05(2H,s),6.79(1H,d,J=1.2Hz),6.91(1H,d,J=1.2Hz),6.98(1H,d,J=1.7Hz),7.16(2H,d,J=8.0Hz),7.24(2H,d,J=8.0Hz),7.30(1H,d,J=1.7Hz).

[Example 33]

[0089]

Production example 33: Synthesis of 3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionitrile [Compound No. 33]

Example 33-1: Synthesis of (4-{[(2-cyano-ethyl)-(4-dipropylamino-butyl)-amino]-methyl}-benzyl)-carbamic acid t-butyl ester

The compound (260 mg) obtained in Example 23-4 was dissolved in methanol (5.0 ml) and added with distilled water (1.0 ml) and

acrylonitrile (87.4 μl) and the whole was stirred overnight at room temperature. After completion of the reaction, the solvent was distilled off and the resultant was subjected to extraction with chloroform and washed with a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (332 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=445$[M+H]^+$

Example 33-2: Synthesis of 3-[(4-(aminomethyl-benzyl)-(4-dipropylamino-butyl)-amino)-propionitrile

The compound (331 mg) obtained in Example 33-1 was dissolved in anhydrous THF (1.0 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (6.0 ml) and the whole was stirred at room temperature for 20 minutes. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution, subjected to extraction with chloroform, and washed with a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (235 mg) as a pale-yellow oily substance.

MS(FAB,Pos.):m/z=345$[M+H]^+$

Example 33-3: Synthesis of 3-[(4-(dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)amino]-propionitrile

The compound (235 mg) obtained in Example 33-2 was dissolved in anhydrous methanol (5.0 ml) and added with trimethyl

orthoformate (112 µl) and 2-imidazole carboxaldehyde (72.1 mg) and the whole was stirred overnight at room temperature under a nitrogen atmosphere. Subsequently, sodium borohydride (25.8 mg) was added thereto in an ice bath and the whole was stirred at room temperature for 2 hours. After completion of the reaction, the resultant was added with distilled water and stirred for a while. The resultant was subjected to extraction with chloroform and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (309 mg) as a pale-yellow oily substance.

MS(FAB,Pos.):m/z=425$[M+H]^+$

Example 33-4: Synthesis of 3-[(4-(dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(5-methyl-cyanopenta-1,3-dienylmethyl)-amino]-methyl}-benzyl)-amino]-propionitrile

The compound (141 mg) obtained in Example 33-3 was dissolved in anhydrous methanol (3.0 ml) and added with sodium cyanoborohydride (31.3 mg), acetic acid (1.00 ml), and 1-methyl-2-imidazole carboxaldehyde (40.2 mg) and the whole was stirred at room temperature for 4 days under a nitrogen atmosphere. After completion of the reaction, the solvent was distilled off and the resultant was dissolved in chloroform and added with a 1 mol/l sodium hydroxide aqueous solution, followed by stirring for a while. The resultant was subjected to extraction with chloroform and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution. The organic

layer was dried with anhydrous sodium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with tartaric acid, thereby obtaining a tartrate (159 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=519[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6+D_2O):δ=0.89(6H,t,J=7.3Hz),1.43-1.46(2H,m),1.55-1.61(6H,m),2.42(2H,t,J=6.7Hz),2.64-2.66(4H,m),2.92-2.97(6H,m),3.51(3H,s),3.53(2H,s),3.55(2H,s),3.61(4H,s),4.22(6H,s),6.86(1H,d,J=1.2Hz),7.05(2H,s),7.11(1H,d,J=1.2Hz),7.28(2H,d,J=8.4Hz),7.31(2H,d,J=8.4Hz).

[Example 34]

[0090]

Production example 34: Synthesis of 3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid methyl ester [Compound No. 34]

Example 34-1: Synthesis of 3-[(4-amino-methyl-benzyl)-(4-dipropylamino-butyl)-amino]-propionic acid methyl ester

The compound (128 mg) obtained in Example 33-1 was dissolved in anhydrous methanol (1.0 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (3.0 ml) and the whole was stirred at room temperature for 2.5 hours. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution, subjected to extraction with chloroform, and washed with a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The

solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (40.6 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=378[M+H]$^+$

Example 34-2: Synthesis of 3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid methyl ester

The compound (40.0 mg) obtained in Example 34-1 was dissolved in anhydrous methanol (1.0 ml) and added with trimethyl orthoformate (17.4 μl) and 2-imidazole carboxaldehyde (11.2 mg) and the whole was stirred overnight at room temperature under a nitrogen atmosphere. Subsequently, sodium borohydride (4.00 mg) was added thereto in an ice bath and the whole was stirred at room temperature for 2 hours.

After completion of the reaction, distilled water was added thereto and the whole was stirred for a while. The resultant was subjected to extraction with chloroform and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (48.2 mg) as a colorless oily substance.

[0091]

Example 34-3: Synthesis of 3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]

-propionic acid methyl ester [Compound No. 34]

The compound (48.2 mg) obtained in Example 34-2 was dissolved in anhydrous methanol (1.0 ml) and added with sodium cyanoborohydride (9.90 mg), acetic acid (100 µl), and 1-methyl-2-imidazole carboxaldehyde (12.8 mg) and the whole was stirred at room temperature for 3 days under a nitrogen atmosphere. After completion of the reaction, the solvent was distilled off. The resultant was dissolved in chloroform and added with a 1 mol/l sodium hydroxide aqueous solution, and the whole was stirred for a while. The solution was subjected to extraction with chloroform, and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (56.1 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=552$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6+D_2O):δ=0.92(6H,t,J=7.3Hz),1.62-1.69(6H,m),1.74-1.83(2H,m),2.92-3.06(10H,m),3.17-3.22(2H,m),3.64(3H,s),3.72(3H,s),3.75(2H,s),4.10(2H,s),4.19(2H,s),4.26-4.34(2H,m),7.41(2H,d,J=8.2Hz),7.465(1H,s),7.467(1H,s),7.50(2H,d,J=8.1Hz),7.60(2H,s).

[Example 35]

[0092]

Production example 35: Synthesis of 1-(4-dipropylamino-butyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-thiou

rea [Compound No. 35]

Example 35-1: Synthesis of
1-(4-cyano-phenyl)-3-(4-dipropylamino-butyl)-thiourea

The compound (656.8 mg) obtained in Example 1-2 was dissolved in anhydrous toluene (19.7 ml) and added with 4-isothiocyanate-benzonitrile (manufactured by Aldrich Corporation) (793.0 mg) and the whole was refluxed under heating for 18.5 hours. After having been left for cooling, the solvent was distilled off. The resultant was added with water and subjected to extraction with chloroform. The resultant was dried with magnesium sulfate and the solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (314.4 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=333$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.83(6H,t,J=7.3Hz),1.34-1.41(4H,m),1.55(2H,quint.,J=6.8Hz),1.71(2H,quint.,J=6.6Hz),2.28(4H,t,J=7.8Hz),2.42(2H,t,J=6.3Hz),3.62(2H,br),7.39(2H,br),7.65(2H,d,J=8.8Hz).

Example 35-2: Synthesis of
1-(4-dipropylamino-butyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-thiourea

The compound (314.4 mg) obtained in Example 35-1 was dissolved in anhydrous THF (12.6 ml) and added with Lithium aluminum hydride (144 mg) and the whole was stirred overnight at room temperature. Then, the solution was refluxed under heating for 2 hours. After completion of the reaction, ethyl acetate was added thereto. An aqueous sodium potassium tartrate

solution was added thereto and the whole was stirred overnight. The resultant was subjected to extraction with chloroform.

The resultant was dried with magnesium sulfate and the solvent was distilled off.

The resultant was dissolved in methanol (6.4 ml) and added with 2-imidazole carboxaldehyde (137.4 mg) and trimethyl orthoformate (0.312 ml) and the whole was stirred at room temperature for 2 hours. Sodium borohydride (107.8 mg) was added thereto and the whole was stirred at room temperature for 1 hour. After completion of the reaction, the solvent was distilled off. The resultant was added with water, subjected to extraction with chloroform, and dried with magnesium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (93.8 mg) as a colorless oily substance.
MS(FAB,Pos.):m/z=417$[M+H]^+$

Example 35-3: Synthesis of 1-(4-dipropylamino-butyl)-3-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-thiourea [Compound No. 35]

The compound (93.8 mg) obtained in Example 35-2 was dissolved in anhydrous methanol (3.8 ml) and added with 1-methyl-2-imidazole carboxaldehyde (38.5 mg) and sodium cyanoborohydride (43.4 mg). The solution was adjusted to pH 5 with acetic acid and stirred at room temperature for 13.5 hours. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform. The resultant was

dried with magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining hydrochloride (86.6 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=511[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6+D_2O):δ=0.91(6H,t,J=7.3Hz),1.56-1.68(8H,m),2.99-3.02(4H,m),3.06-3.09(2H,m),3.50(2H,br),3.66(2H,s),3.70(3H,s),4.04(2H,s),4.12(2H,s),7.26(2H,d,J=8.5Hz),7.40(2H,d,J=8.3Hz),7.50(2H,s),7.61(2H,s).

[Example 36]

[0093]

Production example 36: Synthesis of {3-[6-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-pyridin-2-yl]-propyl}-dipropyl-amine [Compound No. 36]

Example 36-1: Synthesis of 2-chloro-6-p-tolylpyridine

4-Methylphenyl boronic acid (1.00 g), 2,6-dichloropyridine (3.27 g), tetrakis(triphenylphosphine)palladium(0) (0.255 g), and potassium phosphate (3.12 g) were dissolved in toluene (35 ml) and water (6.0 ml). The mixture was stirred at 80°C for 15 hours under a nitrogen atmosphere. The organic layer was separated, washed with a saturated aqueous sodium hydrogen carbonate solution, and dried with anhydrous magnesium sulfate and the solvent was distilled off. The resultant was crudely purified through silica gel column chromatography (chloroform), thereby obtaining a mixture (4.02 g) containing the subject compound.

[0094]

Example 36-2: Synthesis of
2-(4-bromomethyl-phenyl)-6-chloro-pyridine

The mixture (4.02 g) obtained in Example 36-1 in a carbon tetrachloride solution (45 ml) was added with N-bromosuccinimide (1.31 g) and 2,2'-azobisisobutyronitrile (0.121 g) and the whole was refluxed for 30 minutes. After that, the solution was cooled to room temperature and a solid component was separated by filtration. The organic layer was washed with a 1 mol/l sodium hydroxide aqueous solution and a saturated saline solution in the stated order, and dried with anhydrous magnesium sulfate. The solvent was distilled off and dried under reduced pressure, thereby obtaining a mixture (5.72 g) containing the subject compound.

[0095]

Example 36-3: Synthesis of
2-[4-(6-chloro-pyridin-2-yl)-benzyl]-isoindol-1,3-dione

The mixture (5.72 g) obtained in Example 36-2 and potassium phthalimide (2.04 g) were dissolved in DMF (30 ml) and the whole was stirred at room temperature for 24 hours. Then, a solid component was separated by filtration. After the solvent was distilled off, the resultant was dissolved in chloroform and washed with a aqueous sodium hydrogen carbonate solution. The aqueous layer was extracted with chloroform and dried with anhydrous magnesium sulfate. The solvent was distilled off. The resultant residue was purified through silica gel column chromatography (chloroform), thereby obtaining the subject compound (1.56 g)

as a colorless solid.

MS(FAB,Pos.):m/z=349$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=4.90(2H,s),7.25(1H,d,J=7.8Hz),7.53(2H,d,J=8.5Hz),7.60(1H,d,J=7.8Hz),7.68(1H,t,J=7.8Hz),7.72(2H,dd,J=3.2,5.4Hz),7.86(2H,dd,J=2.9,5.4Hz),7.94(2H,d,J=8.3Hz).

Example 36-4: Synthesis of 2-{4-[6-(3-dipropylamino-propyl)-pyridin-2-yl]-benzyl}-isoindol-1,3-dione

An anhydrous THF solution (1.0 ml) containing 2-propenyl dipropylamine (158 mg) was cooled with ice and a 0.5 mol/l 9-borabicyclo-[3,3,1]-nonane(9-BBN)/THF solution (2.06 ml) was dropped thereto. The whole was gradually warmed to room temperature and stirred for 5 hours. After that, a 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex ($PdCl_2$(dppf)) (210 mg) and the compound (300 mg) obtained in Example 36-3 were added thereto together with DMF (3.0 ml), and a 3 mol/l aqueous solution (0.86 ml) of cesium fluoride was added thereto. The whole was stirred at 80°C for 23 hours and then heated to 100°C and stirred for 2 hours. After the resultant was cooled to room temperature, a solid component was separated by filtration and the solvent was distilled off. The concentrate was dissolved in chloroform, washed with saturated aqueous sodium hydrogen carbonate solution, extracted with chloroform, and dried with anhydrous magnesium sulfate, followed by distillating off the solvent. The resultant residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (44.0 mg) as a pale-brown liquid.

MS(FAB,Pos.):m/z=456[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.87(6H,t,J=7.3Hz),1.42-1.70(4H,m),1.98-2.16(2H,m),2.40-2.80(6H,m),2.86(2H,t,J=7.6Hz),4.90(2H,s),7.08(1H,d,J=7.3Hz),7.50(1H,d,J=7.8Hz),7.52(2H,d,J=8.5Hz),7.63(1H,t,J=7.8Hz),7.72(2H,dd,J=3.2,5.6Hz),7.86(2H,dd,J=3.2,5.4Hz),7.93(2H,d,J=8.3Hz).

Example 36-5: Synthesis of {3-[6-(4-aminomethyl-phenyl)-pyridin-2-yl]-propyl}-dipropyl-amine

A methanol solution (2.0 ml) containing the compound (40.0 mg) obtained in Example 36-4 was added with hydrazine monohydrate (44 mg) and the whole was stirred at 60°C for 1.5 hours, followed by distillating off the solvent. The residue was dissolved in chloroform and filtrated through Celite, the solvent was distilled off, thereby obtaining the subject compound (30.1 mg) as an amber liquid.

[0096]

Example 36-6: Synthesis of {3-[6-(4-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-pyridin-2-yl]-propyl}-dipropyl-amine

An anhydrous methanol solution (0.50 ml) containing the compound (30.1 mg) obtained in Example 36-5 and 2-imidazole carboxaldehyde (10.1 mg) was added with trimethyl orthoformate (0.029 ml), and the whole was stirred at room temperature for 14 hours. Sodium borohydride (17.0 mg) was added thereto and the whole was stirred for 30 minutes. The solvent was distilled off. The residue was dissolved in chloroform, washed with a

saturated aqueous sodium hydrogen carbonate solution, and dried with anhydrous sodium sulfate, and the solvent was distilled off, thereby obtaining the subject compound (30.4 mg).

[0097]

Example 36-7: Synthesis of {3-[6-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-pyridin-2-yl]-propyl}-dipropyl-amine [Compound No. 36]

An anhydrous methanol solution (0.50 ml) containing the compound (30.4 mg) obtained in Example 36-6 and 1-methyl-2-imidazole carboxaldehyde (11.6 mg) was added with 4 drops of acetic acid. Then, sodium cyanoborohydride (17 mg) was added thereto and the whole was stirred at room temperature for 29 hours. After completion of the reaction, the solvent was distilled off. The residue was dissolved in chloroform, washed with a saturated aqueous sodium hydrogen carbonate solution, and dried with anhydrous sodium sulfate, and the solvent was distilled off. The resultant residue was purified through silica gel column chromatography (chloroform), thereby obtaining the subject compound (23.0 mg) as a pale-yellow viscous liquid. The liquid was treated with hydrochloric acid, thereby obtaining a hydrochloride (28.3 mg) of the subject compound as a colorless solid.

MS(FAB,Pos.):m/z=500$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.88(6H,t,J=7.3Hz),1.46(4H,sext.,J=7.6Hz),1.97(2H,quint.,J=7.6Hz),2.40(4H,t,J=7.6Hz),2.53(2H,t,J=7.3Hz),2.86(2H,t,J=7.6Hz),3.49(2H,s),3.59(3H,s),3.66(2H,s),3.75(2H,s),6.89(1H,d,J=2.2Hz),7.01(1H,d,J=2.0Hz),7.10(1H,d,J=7.1Hz),7.10(1H,br),7.15(1H,br),7.51(2H,d,J=8.3Hz),7.53(1H,d,J

=7.8Hz),7.65(1H,t,J=7.8Hz),7.99(2H,d,J=8.3Hz),12.40(1H,s).

[Example 37]

[0098]

Production example 37: Synthesis of N-(4-dipropylamino-butyl)-2,2,2-trifluoro-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-acetamide [Compound No. 37]

Example 37-1: Synthesis of N-(4-dipropylamino-butyl)-2,2,2-trifluoro-N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-acetamide [Compound No. 37]

The compound (166.6 mg) obtained in Example 21-4 was dissolved in anhydrous dichloromethane (5.0 ml) and added with triethylamine (0.052 ml). The whole was cooled with ice and added with trifluoroacetic anhydride (0.052 ml), followed by stirring at room temperature for 1 hour. After completion of the reaction, the resultant was washed with water and dried with magnesium sulfate. The solvent was distilled off.

The resultant was dissolved in methanol (2.4 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (2. 4 ml) and the whole was stirred at room temperature for 1 hour. After completion of the reaction, the solvent was distilled off. A 1 mol/l sodium hydroxide aqueous solution was added thereto and the whole was subjected to extraction with chloroform and dried with magnesium sulfate. The solvent was distilled off.

The resultant was dissolved in anhydrous methanol (6.5 ml) and added with 2-imidazole carboxaldehyde (49.0 mg) and sodium cyanoborohydride (64.1 mg). The solution was adjusted to pH 5

with acetic acid and stirred at room temperature for 3 days. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform. The resultant was dried with magnesium sulfate and the solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining hydrochloride (84.9 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=562[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6+D_2O):δ=0.90(6H,dt,J=3.1,7.3Hz),1.57-1.67(8H,m),2.95-3.03(6H,m),3.24(1H,m),3.35(1H,m),3.69(3H,s),3.71(2H,s),4.07(2H,d,J=5.8Hz),4.15(2H,d,J=8.7Hz),4.57(1H,s),4.63(1H,s),7.12-7.17(2H,m),7.31-7.35(2H,m),7.45(2H,s),7.58(2H,s).

[Example 38]

[0099]

Production example 38: Synthesis of [4-(5-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1,3-dihydro-isoindol-2-yl)-butyl]-dipropyl-amine [Compound No. 38]

Example 38-1: Synthesis of [4-(5-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-1,3-dihydro-isoindol-2-yl)-butyl]-dipropyl-amine

A THF solution (2.0 ml) containing the compound (24.3 mg) obtained in Example 7-7 was added with a 1 mol/l borane-THF complex/THF solution (0.41 ml). The whole was refluxed under heating for 16 hours. After having been cooled to 0°C, the solution

was added with methanol to stop the reaction and concentrated. The residue was added with a 1 mol/l hydrochloric acid (4.0 ml) and the whole was refluxed under heating for 3 hours. After having been left standing for cooling, the resultant was added with a 1 mol/l sodium hydroxide aqueous solution (5 ml) and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and dried with anhydrous sodium sulfate. The residue obtained by distilling the solvent off was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (12.5 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=384$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.88(6H,t,J=7.3Hz),1.42-1.48(4H,m),1.49-1.60(4H,m),2.36-2.39(4H,m),2.45(2H,t,J=7.3Hz),2.72(2H,t,J=7.3Hz),3.76(2H,s),3.88-3.90(6H,m),6.98(2H,s),7.10-7.15(3H,m).

Example 38-2: Synthesis of [4-(5-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1,3-dihydro-isoindol-2-yl)-butyl]-dipropyl-amine [Compound No. 38]

The compound (12.5 mg) obtained in Example 38-1 was dissolved in methanol (2.0 ml) and added with 1-methyl-2-imidazole carboxaldehyde (4.4 mg) and sodium cyanoborohydride (4.2 mg). The solution was adjusted to pH 4 with acetic acid and stirred at room temperature for 8 hours. The residue obtained by concentration of the solution was added with a saturated aqueous sodium hydrogen carbonate solution to neutralize the solution and the whole was subjected to extraction with chloroform. The

organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and dried with anhydrous sodium sulfate. The residue obtained by distilling the solvent off was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (7.7 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=478[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.87(6H,t,J=7.4Hz),1.42-1.48(4H,m),1.49-1.60(4H,m),2.35(4H,m),2.45(2H,t,J=7.3Hz),2.72(2H,t,J=7.3Hz),3.43(2H,s),3.54(3H,s),3.62(2H,s),3.67(2H,s),3.90(4H,s),6.87(1H,d,J=1.5Hz),7.00(1H,d,J=1.2Hz),7.08(1H,s),7.12(1H,s),7.15(1H,d,J=8.0Hz),7.23-7.24(3H,m),12.38(1H,br).

[Example 39]

[0100]

Production example 39: Synthesis of {4-(1E)-[2-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-vinyl]-benzyl}-dipropyl-amine [Compound No. 39]

Example 39-1: Synthesis of methylen-triphenyl-λ^5-phosphane

Methyl triphenyl phosphinium bromide (6.00 g) was suspended in THF (50 ml). After having been cooled to 0°C, the reaction solution was added with sodium amide (1.46 g) and the whole was refluxed under heating for 3 hours. The reaction solution was cooled to room temperature and then filtrated through Celite. The filtrate was concentrated under reduced pressure, thereby obtaining the subject compound (1.92 g) as a yellow-red solid.

[0101]

Example 39-2: Synthesis of 2-(4-vinyl-benzyl-isoindol)-1,3-dione

The compound (0.99 g) obtained in Example 1-1 was dissolved in THF (30 ml). The reaction solution was cooled to 0°C and added with the compound (1.66 g) obtained in Example 39-1 and the whole was stirred at room temperature for 1.5 hours. The reaction solution was concentrated under reduced pressure and the solvent was distilled off. The resultant residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (0.78 g) as a white solid. ^{1}H-NMR(500MHz,$CDCl_3$):δ=4.83(2H,s),5.23(1H,dd,J=1.0,10.0Hz),5.71(1H,dd,J=1.0,16.6Hz),6.67(1H,dd,J=6.8,10.7Hz),7.35-7.40(4H,m),7.70-7.72(2H,m),7.83-7.85(2H,m).

Example 39-3: Synthesis of 4-{2-[4-(1E)-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-phenyl]-vinyl}-benzaldehyde

The compound (760 mg) obtained in Example 39-2, p-bromobenzaldehyde (690 mg), tri-o-tolylphosphine (103 mg), and palladium acetate (39 mg) were suspended in xylene (15 ml) and triethylamine (15 ml) and the whole was stirred at 130°C for 63 hours. The reaction solution was cooled to room temperature and then the solvent was concentrated under reduced pressure. The resultant residue was added with distilled water and the whole was subjected to extraction with dichloromethane. The organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure. The residue was purified through silica

gel column chromatography (hexane/dichloromethane), thereby obtaining a yellow-white solid (0.91 g).

MS(FAB,Pos.):m/z=368[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=4.86(2H,s),7.11(1H,d,J=16.2Hz),7.22(1H,d,J=16.2Hz),7.45(2H,d,J=8.3Hz),7.50(2H,d,J=8.3Hz),7.64(2H,d,J=8.5Hz),7.71-7.73(2H,m),7.85-7.87(4H,m),9.99(1H,s).

Example 39-4: Synthesis of 2-{4-(1E)-[2-(4-dipropylaminomethyl-phenyl)-vinyl]-benzyl}-isoindol-1,3-dione

The compound (650 mg) obtained in Example 39-3 was dissolved in 1,2-dichloroethane (40 ml). The reaction solution was added with n-dipropylamine (0.29 ml) and sodium triacetoxyborohydride (600 mg) and the whole was stirred at room temperature for 18 hours. After that, n-dipropylamine (0.29 ml) was added thereto and the whole was stirred at 50°C for 1 hour. Then, sodium triacetoxyborohydride (600 mg) was added thereto and the whole was stirred at 50°C for 20 hours. After the reaction solution was cooled to room temperature, the solvent was concentrated under reduced pressure. The resultant residue was added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform. The organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (646 mg) as a white solid.

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.3Hz),1.44-1.51(4H,m),2.35-2.38(4H,m),3.54(2H,s),4.85(2H,s),7.05(2H,d,J=1.7Hz),7.30-7

.46(8H,m),7.70-7.73(2H,m),7.84-7.86(2H,m).

Example 39-5: Synthesis of {4-(1E)-[2-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-phenyl)-vinyl]-benzyl}-dipropyl-amine [Compound No. 39]

The compound (630 mg) obtained in Example 39-4 was dissolved in chloroform (5.0 ml) and methanol (10 ml). The reaction solution was added with hydrazine monohydrate (1.0 ml) and refluxed under heating for 1 hour. The reaction solution was cooled to room temperature and then the precipitated solid was filtrated out. The filtrate was concentrated under reduced pressure. The residue was added with distilled water and the whole was subjected to extraction with chloroform. The organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure.

The resultant was dissolved in methanol (12 ml). The reaction solution was added with 2-imidazole carboxaldehyde (219 mg) and trimethyl orthoformate (0.39 ml) and the whole was stirred at room temperature for 16 hours. After having been cooled to 0°C, the reaction solution was added with sodium borohydride (135 mg) and the whole was stirred at room temperature for 3 hours. The reaction solution was concentrated under reduced pressure. The resultant residue was added with distilled water and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure.

The resultant was dissolved in methanol (12 ml). The

reaction solution was added with 1-methyl-2-imidazole carboxaldehyde (156 mg) and trimethyl orthoformate (0.24 ml) and the whole was stirred at room temperature for 15 hours. After having been cooled to 0°C, the reaction solution was added with sodium borohydride (83 mg) and the whole was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure. The resultant residue was added with distilled water and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (449 mg) as a white solid.

MS(FAB,Pos.):m/z=497$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.88(6H,t,J=7.3Hz),1.70(4H,tq,J=7.3,7.6Hz),2.96(4H,t,J=7.6Hz),3.17(2H,s),3.72(3H,s),4.07(2H,s),4.15(2H,s),4.31(2H,s),7.28(2H,d,J=9.9Hz),7.35(2H,d,J=8.1Hz),7.50(2H,s),7.52-7.57(4H,m),7.62(2H,s),7.69(2H,d,J=8.2Hz).

[Example 40]

[0102]

Production example 40: Synthesis of {[4-((1Z)-2-{4-[(dipropylamino)-methyl]-phenyl}-vinyl)-phenyl]-methyl}-(imidazol-2-ylmethyl)-[(1-methylimidazol-2-yl)-methyl]-amine [Compound No. 40]

Example 40-1: Synthesis of 4-((1Z)-2-{4-[(1,3-dioxo[c]azolin-2-yl)-methyl]-phenyl}-vinyl)-benzaldehyde

The compound (0.76 g) obtained in Example 39-3, p-bromobenzaldehyde (0.69 g), tri-o-tolylphosphine (103 mg), and palladium acetate (39 mg) were suspended in xylene (15 ml) and triethylamine (15 ml) and the whole was stirred at 130°C for 63 hours. The reaction solution was cooled to room temperature and then the solvent was concentrated under reduced pressure. The resultant residue was added with distilled water and the whole was subjected to extraction with dichloromethane. The organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure. The resultant residue was purified through silica gel column chromatography (hexane/dichloromethane), thereby obtaining the subject compound (25 mg) as a colorless oily substance.

^{1}H-NMR(500MHz,$CDCl_3$):δ=4.87(2H,s),5.55(2H,m),7.72-7.88(8H,m), 7.25-7.48(4H,m),10.02(1H,s).

Example 40-2: Synthesis of 2-{[4-((1Z)-2-{4-[(dipropylamino)-methyl]-phenyl}-vinyl)-phenyl]-methyl}-benzo[c]azolin-1,3-dione

The compound (25 mg) obtained in Example 40-1 was dissolved in 1,2-dichloroethane (3.0 ml). The reaction solution was added with n-dipropylamine (0.019 ml) and sodium triacetoxyborohydride (36 mg) and the whole was stirred at room temperature for 62 hours. After that, n-dipropylamine (0.019 ml) and sodium triacetoxyborohydride (36 mg) were added thereto and the whole was stirred at 50°C for 3 hours. Then, n-dipropylamine (0.019 ml) and sodium triacetoxyborohydride (36 mg) were added thereto and the whole was refluxed under heating for 3 hours. After the

reaction solution was cooled to room temperature, the solvent was concentrated under reduced pressure. The resultant residue was added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform. The organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure. The resultant residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (27.0 mg) as a colorless oily substance.
^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.3Hz),1.44-1.50(4H,m),2.36-2.39(4H,m),3.55(2H,s),4.86(2H,s),5,37(1H,d,J=1.2Hz),5.44(1H,d,J=1.2Hz),7.22-7.47(6H,m),7.70-7.74(2H,m),7.84-7.87(2H,m).

Example 40-3: Synthesis of {[4-((1Z)-2-{4-[(dipropylamino)-methyl]-phenyl}-vinyl)-phenyl]-methyl}-(imidazol-2-ylmethyl)-[(1-methylimidazol-2-yl)-methyl]-amine [Compound No. 40]

The compound (110 mg) obtained in Example 40-2 was dissolved in methanol (6.0 ml). The reaction solution was added with hydrazine monohydrate (0.5 ml) and refluxed under heating for 1 hour. The reaction solution was cooled to room temperature and then the solvent was concentrated under reduced pressure. The resultant residue was added with distilled water and the whole was subjected to extraction with chloroform. The organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure.

The resultant was dissolved in methanol (3.0 ml).

2-Imidazole carboxaldehyde (16.4 mg) and trimethyl orthoformate (28 μl) were added thereto, and the whole was stirred at room temperature for 16.5 hours. After having been cooled to 0°C, the reaction solution was added with sodium borohydride (9.7 mg) and the whole was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure. The resultant residue was added with distilled water and the whole was subjected to extraction with chloroform. The organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure.

The resultant was dissolved in methanol (2.0 ml) and added with 1-methyl-2-imidazole carboxaldehyde (9.5 mg) and trimethyl orthoformate (14 μl), and the whole was stirred at room temperature for 65 hours. After having been cooled to 0°C, the reaction solution was added with sodium borohydride (4.1 mg) and the whole was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure. The resultant residue was added with distilled water and the whole was subjected to extraction with chloroform. The organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (3.9 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=497$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.87(6H,t,J=7.3Hz),1.49(4H,tq,J=7.3,7.6Hz),2.39(4H,t,J=7.6Hz),3.50(2H,s),3.56(3H,s),3.59(2H,s),3.63(2H,s),3.71(2H,s),5.42(1H,d,J=1.2Hz),5.44(1H,d,J=1.2Hz),6.8

8-7.47(12H,m).

[Example 41]

[0103]

Production example 41: Synthesis of {[4-((1E)-2-{4-[2-(dipropylamino)-ethyl]-phenyl}-vinyl)-phenyl]-methyl}-(imidazol-2-ylmethyl)-[(1-methylimidazol-2-yl)-methyl]-amine [Compound No. 41]

Example 41-1: Synthesis of 2-{[4-((1E)-2-{4-[2-(dipropylamino)-ethyl]-phenyl}-vinyl)-phenyl]-methyl}-benzo[c]azolin-1,3-dione

Under a nitrogen atmosphere, methoxymethyl triphenylphosphonium chloride (1.05 g) was suspended in THF (25 ml). After having been cooled to 0°C, the reaction solution was added with a 2 mol/l lithium diisopropylamide/heptane/THF/ethylbenzene solution (1.52 ml) and the whole was stirred at room temperature for 1.5 hours to control ylide. Under a nitrogen atmosphere, the compound (400 mg) obtained in Example 39-4 was suspended in THF (20 ml). After having been cooled to 0°C, the reaction solution was added with ylide and the whole was stirred at room temperature for 14 hours. The reaction solution was concentrated under reduced pressure and then the residue was purified through column chromatography (chloroform/ethyl acetate).

The resultant was dissolved in 1,4-dioxane (10 ml). The reaction solution was added with 1 mol/l hydrochloric acid (3.0 ml) and the whole was refluxed under heating for 2 hours. The reaction solution was cooled to room temperature and the solvent was then concentrated under reduced pressure. A 1 mol/l sodium

hydroxide aqueous solution was added thereto and the whole was subjected to extraction with chloroform. After that, the organic layer was washed with a saturated saline solution and the organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure.

The resultant was dissolved in 1,2-dichloroethane (6.0 ml). The reaction solution was added with n-dipropylamine (0.057 ml) and sodium triacetoxyborohydride (106 mg), and the whole was stirred at room temperature for 66 hours. After having been concentrated under reduced pressure, the reaction solution was added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform.

The organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure. The resultant residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (55 mg) as a white solid.

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.82-0.94(6H,m),1.44-1.65(4H,m),2.48(4H,t,J=7.6Hz),4.85(2H,s),7.04(2H,d,J=3.9Hz),7.16-7.49(8H,m),7.65-7.73(2H,m),7.84-7.86(2H,m).

Example 41-2: Synthesis of {[4-((1E)-2-{4-[2-(dipropylamino)-ethyl]-phenyl}-vinyl)-phenyl]-methyl}-(imidazol-2-ylmethyl)-[(1-methylimidazol-2-yl)-methyl]-amine [Compound No. 41]

The compound (113 mg) obtained in Example 41-1 was dissolved in chloroform (5.0 ml) and methanol (5.0 ml).

The reaction solution was added with hydrazine monohydrate (0.5 ml) and refluxed under heating for 2 hours. The reaction solution was cooled to room temperature and then the solvent was concentrated under reduced pressure. The resultant residue was added with distilled water and the whole was subjected to extraction with chloroform. The organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure.

The resultant was dissolved in methanol (5.0 ml). 2-Imidazole carboxaldehyde (41 mg) and trimethyl orthoformate (0.065 ml) were added thereto and the whole was stirred at room temperature for 15.5 hours. After having been cooled to 0°C, the reaction solution was added with sodium borohydride (22 mg) and the whole was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure. The resultant was added with distilled water and the whole was subjected to extraction with chloroform. The organic layer was dried with anhydrous magnesium sulfate.

The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure.

The resultant was dissolved in methanol (37 ml). 1-Methyl-2-imidazole carboxaldehyde (9.5 mg) and trimethyl orthoformate (0.051 ml) were added thereto and the whole was stirred at room temperature for 16 hours. After having been cooled to 0°C, the reaction solution was added with sodium borohydride (18 mg) and the whole was stirred at room temperature for 3 hours. The reaction solution was concentrated under reduced pressure. The resultant was added with distilled water and the whole was subjected to extraction with chloroform. The organic layer was

dried with anhydrous magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (65.4 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=511[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.92(6H,t,J=7.3Hz),1.71(4H,sext.,J=7.3Hz),3.02-3.08(6H,m),3.20-3.26(2H,m),3.64-3.72(2H,m),3.71(3H,s),4.09(2H,s),4.16(2H,s),7.21(2H,s),7.32(2H,d,J=8.2Hz),7.40(2H,d,J=8.2Hz),7.49(2H,d,J=8.4Hz),7.52-7.56(4H,m),7.65(2H,s),10.45(1H,br).

[Example 42]

[0104]

Production example 42: Synthesis of {[4-((1E)-2-{4-[(dipropylamino)-methyl]-phenyl}-vinyl)-phenyl]-methyl}-bis-(imidazol-2-ylmethyl)-amine [Compound No. 42]

Example 42-1: Synthesis of {[4-((1E)-2-{4-[(dipropylamino)-methyl]-phenyl}-vinyl)-phenyl]-methyl}-bis-(imidazol-2-ylmethyl)-amine [Compound No. 42]

The compound (311 mg) obtained in Example 39-4 was dissolved in chloroform (5.0 ml) and methanol (5.0 ml).

The reaction solution was added with hydrazine monohydrate (0.5 ml) and refluxed under heating for 2 hours. The reaction solution was cooled to room temperature and then the solvent was concentrated under reduced pressure. The resultant was added with distilled water and the whole was subjected to extraction with chloroform. The organic layer was dried with anhydrous

magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure.

The resultant was dissolved in methanol (8.0 ml). After having been cooled to 0°C, the reaction solution was added with 2-imidazole carboxaldehyde (128 mg), trimethyl orthoformate (0.146 ml), and sodium cyanoborohydride (107 mg) and the whole was stirred at room temperature for 38 hours. The reaction solution was concentrated under reduced pressure. The resultant residue was added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform. The organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtrated out and the organic layer was then concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (50 mg) of the subject compound as a yellow-white solid.

MS(FAB,Pos.):m/z=483[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.87(6H,t,J=7.3Hz),1.72(4H,br),2.93(4H,br),4.13(2H,s),4.30(4H,br),4.48(2H,br),7.28(1H,d,J=7.3Hz),7.38(1H,s),7.43(1H,d,J=8.1Hz),7.50(1H,d,J=8.2Hz),7.59-7.71(10H,m).

[Example 43]

[0105]

Production example 43: Synthesis of [4-(6-{[(1H-imidazol-2-yl-methyl)-(1-methyl-imidazol-2-yl-methyl)-amino]-methyl}-benzothiazol-2-yl)-benzyl]-dipropyl-amine [Compound No. 43]

Example 43-1: Synthesis of
N-(4-cyano-phenyl)-4-methyl-benzamide

4-Aminobenzonitrile (1.10 g) was dissolved in chloroform (30 ml). After having been cooled to 0°C, the reaction solution was added with 4-dimethylaminopyridine (1.70 g) and p-toluic acid chloride (1.95 g). The reaction solution was warmed back to room temperature and stirred overnight. The reaction solution was added with distilled water and subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure. The resultant residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and then purified by recrystallization (hexane/ethanol), thereby obtaining the subject compound (1.26 g) as a white solid.
MS(FAB,Pos.):m/z=237$[M+H]^+$

Example 43-2: Synthesis of
N-(4-cyano-phenyl)-4-methyl-thiobenzamide

The compound (1.26 g) obtained in Example 43-1 was dissolved in toluene (20 ml) and added with a Lawesson's reagent (1.29 g) and the whole was refluxed under heating for 2 hours. The reaction solution was cooled to room temperature and the precipitated solid was filtrated out. The resultant solid was subjected to recrystallization (methanol), thereby obtaining the subject compound (1.09 g) as a yellow solid.
MS(FAB,Pos.):m/z=253$[M+H]^+$

Example 43-3: Synthesis of

2-p-toluyl-benzothiazol-6-carbonitrile

Potassium ferricyanide (5.78 g) was dissolved in distilled water (40 ml) and the whole was heated to 90°C. A suspension containing the compound (1.09 g) obtained in Example 43-2, ethanol (1.0 ml), and a 30% sodium hydroxide aqueous solution (3.2 ml) was dropped to the reaction solution for 5 minutes. The whole was stirred at 90°C for 3 hours and then cooled to room temperature. The precipitated solid was filtrated out and purified by recrystallization (methanol), thereby obtaining the subject compound (0.53 g) as a white solid.

MS(FAB,Pos.):m/z=251$[M+H]^+$

Example 43-4: Synthesis of 2-(4-dipropyl-amino-methyl-phenyl)-benzothiazol-6-carbonitrile

The compound (0.53 g) obtained in Example 43-3 and N-bromosuccinimide (0.43 g) were weighed and carbon tetrachloride (15 ml) was added thereto. The reaction solution was added with 2,2'-azobisisobutyronitrile (13.2 ml) and refluxed under heating for 1.5 hours. The reaction solution was cooled to room temperature and then subjected to filtration through Celite. The filtrate was concentrated under reduced pressure.

The resultant was dissolved in dichloromethane (18 ml) and added with 4-dimethylaminopyridine (0.55 g) and n-dipropylamine (0.5 ml) and the whole was stirred at room temperature for 2 hours. The reaction solution was added with distilled water and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The organic layer was then

concentrated under reduced pressure. The resultant residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (110.2 mg) as a pale-yellow solid.
MS(FAB,Pos.):m/z=350$[M+H]^+$

Example 43-5: Synthesis of
[4-(6-amino-methyl-benzothiazol-2-yl)-benzyl]-dipropyl-amine

The compound (99.8 mg) obtained in Example 43-4 was dissolved in chloroform (1.0 ml) and methanol (10 ml).

The reaction solution was added with platinum oxide (7.3 mg) and the whole was stirred overnight at room temperature under a hydrogen atmosphere. The catalyst was filtrated out through Celite and the filtrate was concentrated under reduced pressure. The resultant residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (52.5 mg) as a pale-yellow solid.
MS(FAB,Pos.):m/z=354$[M+H]^+$

Example 43-6: Synthesis of
[4-(6-{[(1H-imidazol-2-yl-methyl)-(1-methyl-imidazol-2-yl-methyl)-amino]-methyl}-benzothiazol-2-yl)-benzyl]-dipropyl-amine [Compound No. 43]

The compound (52.5 mg) obtained in Example 43-5 was dissolved in methanol (1.0 ml). The reaction solution was added with 2-imidazole carboxaldehyde (15.2 mg) and trimethyl orthoformate (40 µl) and the whole was stirred at room temperature for 2 hours. Subsequently, sodium borohydride (15.3 mg) was added thereto and the whole was stirred at room temperature for 40 minutes. The

reaction solution was added with a saturated aqueous ammonium chloride solution (2.0 ml) and the whole was stirred at room temperature for 30 minutes. The whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The reaction solution was concentrated under reduced pressure.

The resultant was dissolved in methanol (1.5 ml) and added with 1-methyl-2-imidazole carboxaldehyde (37.0 mg) and sodium cyanoborohydride (47.4 mg). The reaction solution was added with acetic acid to adjust to pH 5 and the whole was stirred at room temperature for 20 hours. The reaction solution was added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate.

After the organic layer was concentrated under reduced pressure, the residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (44.8 mg) of the subject compound as a pale-yellow solid.

MS(FAB,Pos.):m/z=528[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.87(6H,t,J=7.3Hz),1.75(4H,br),2.96(4H,br),3.72(3H,s),3.86(2H,s),4.14(2H,s),4.21(2H,s),4.40(2H,br),7.51(2H,s),7.57(1H,d,J=8.3Hz),7.63(2H,s),7.83(2H,d,J=8.4Hz),7.95(1H,d,J=8.3Hz),8.16(2H,d,J=8.4Hz),8.30(1H,s).

[Example 44]

[0106]

Production example 44: Synthesis of

(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-methyl-(4-piperidin-1-ylbutyl)amine [Compound No. 44]

Example 44-1: Synthesis of 4-[(4,4-diethoxybutylamino)methyl]-benzonitrile

4-Formylbenzonitrile (612.0 mg) was dissolved in methanol (18.4 ml), and 4,4-diethoxybutylamine (752.5 mg) and trimethyl orthoformate (1.53 ml) were added thereto. The whole was stirred at room temperature for 18 hours. Subsequently, the solution was added with sodium borohydride (529.7 mg) under ice-cooling and stirred at room temperature for additional 30 minutes. The reaction solution was concentrated under reduced pressure. The residue was added with water and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (1.16 g) as a yellow oily substance.

MS(FAB,Pos.):m/z=277[M+H]$^+$

Example 44-2: Synthesis of 4-{[(4,4-diethoxybutyl)methylamino]methyl}benzonitrile

The compound (1.16 g) obtained in Example 44-1 was dissolved in methanol (34.8 ml) and added with sodium cyanoborohydride (1.21 g) and a 36% formaldehyde aqueous solution (0.648 ml). The solution was adjusted to pH 4 with acetic acid and stirred at room temperature for 18 hours. The reaction solution was concentrated under reduced pressure. The residue was dissolved

in chloroform and washed with a 1 mol/l sodium hydroxide aqueous solution and dried with anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (1.22 g) as a yellow oily substance.

MS(FAB,Pos.):m/z=291[M+H]$^+$

Example 44-3: Synthesis of
4-{[methyl-(4-oxobutyl)-amino]-methyl}-benzonitrile

The compound (1.22 g) obtained in Example 44-2 was dissolved in THF (12.2 ml) and added with 1 mol/l hydrochloric acid (12.2 ml). The whole was stirred at room temperature for 19 hours. The reaction solution was concentrated under reduced pressure. The residue was added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (0.790 g) as a yellow oily substance.

MS(FAB,Pos.):m/z=217[M+H]$^+$

Example 44-4: Synthesis of
4-{methyl-(4-piperidi-1-ylbutyl)-amino]-methyl}-benzonitrile

The compound (0.790 g) obtained in Example 44-3 was dissolved in methanol (23.7 ml) and added with piperidine (0.542 ml) and sodium cyanoborohydride (459.3 mg). The solution was adjusted

to pH 4 with acetic acid and stirred at room temperature for 5 days. The reaction solution was concentrated under reduced pressure. The residue was dissolved in chloroform, washed with a 1 mol/l sodium hydroxide aqueous solution and a saturated saline solution, and dried anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (0.905 g) as a yellow oily substance.

MS(FAB,Pos.):m/z=286$[M+H]^+$

Example 44-5: Synthesis of (4-aminomethylbenzyl)-methyl-(4-piperidin-1-ylbutyl)-amine

Lithium aluminum hydride (360.8 mg) was suspended in THF (27 ml) and a THF solution (27 ml) in which the compound (904.6 mg) obtained in Example 44-4 was dissolved was gradually added thereto. The whole was stirred at room temperature for 1 hour. The reaction solution was added with ethyl acetate, methanol, and a 10% aqueous sodium potassium tartrate solution and the whole was stirred for 1 day. The solution was subjected to extraction with chloroform and washed with a saturated saline solution. After that, the resultant was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (247.5 mg) as a yellow oily substance.

[0107]

Example 44-6: Synthesis of

(4-{[(1H-imidazol-2-ylmethyl)-amino]-methyl)-benzyl}-methyl-(4-piperidin-1-ylbutyl)-amine

The compound (248.5 mg) obtained in Example 44-5 was dissolved in methanol (12.4 ml) and added with 2-imidazole carboxaldehyde (123.7 mg) and trimethyl orthoformate (0.282 ml) and the whole was stirred at room temperature for 2.5 hours. Subsequently, sodium borohydride (97.4 mg) was added thereto under ice-cooling and the whole was stirred at room temperature for additional 30 minutes. The reaction solution was concentrated under reduced pressure. The residue was added with water and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (116.3 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=370$[M+H]^+$

Example 44-7: Synthesis of (4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-methyl-(4-piperidin-1-ylbutyl)amine [Compound No. 44]

The compound (116.3 mg) obtained in Example 44-6 was dissolved in methanol (5.81 ml) and added with 1-methyl-2-imidazole carboxaldehyde (52.0 mg) and sodium cyanoborohydride (39.6 mg). The solution was adjusted to pH 4 with acetic acid and stirred at room temperature for 6 days. The reaction solution was concentrated under reduced pressure. The

residue was dissolved in chloroform, washed with a 1 mol/l sodium hydroxide aqueous solution and a saturated saline solution, and dried with anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (163.4 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=464[M+H]$^+$

^{1}H-NMR(500Mz,DMSO-d_6+D_2O):δ=1.69-1.81(10H,m),2.58(3H,m),2.82-3.17(6H,m),3.71(3H,s),3.74(2H,s),4.11(2H,s),4.19(2H,s),4.31(2H,s),7.41(2H,d,J=8.1Hz),7.47(2H,d,J=8.1Hz),7.50(2H,s),7.62(2H,s).

[Example 45]

[0108]

Production example 45: Synthesis of 2-(2-(4-dipropylamino-butyl)-6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzimidazol-1-yl)-ethanol [Compound No. 45]

Example 45-1: Synthesis of 1-iodo-2-methoxymethoxy-ethane

2-Iodoethanol (0.637 g) was dissolved in dimethoxymethane (5.0 ml). The reaction solution was added with p-toluenesulfonic acid monohydrate (82 mg) and lithium bromide (42 mg), and stirred at room temperature for 18 hours. The reaction solution was concentrated under reduced pressure. The resultant residue was added with distilled water and the whole was subjected to extraction with chloroform. The organic layer was dried with anhydrous sodium sulfate. The drying agent was filtrated out and the organic layer was concentrated under reduced pressure,

thereby obtaining the subject compound (0.547 g) as a brown oily substance.

MS(FAB,Pos.):m/z=217[M+H]$^+$

Example 45-2: Synthesis of 3,4-diamino-benzonitrile

3-Nitro-4-amino-benzonitrile (4.38 g) was dissolved in ethanol (600 ml) and added with stannous chloride dihydrate (34.6 g) and the whole was heated to 60°C. Sodium borohydride (366 mg) was gradually added thereto and the whole was stirred overnight at 60°C. After completion of the reaction, the resultant was filtrated through Celite and the filtrate was subjected to distillation of the solvent under reduced pressure. The residue was dissolved in chloroform, washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution, and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was allowed to recrystallize (hexane/ethyl acetate), thereby obtaining the subject compound (2.56 g) as a brown crystal.

MS(EI):m/z=133[M]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=6.68(1H,d,J=8.1Hz),6.95(1H,s),7.05(1H,d,J=8.1Hz).

Example 45-3: Synthesis of [4-(2-amino-5-cyano-phenylcarbamoyl)-butyl]-carbamic acid t-butyl ester

In chloroform/DMF (60 ml/30 ml), t-butoxycarbonylamino valeric acid (3.91 g), WSCI hydrochloride (4.02 g), and HOBt (2.82 g) were dissolved and the whole was stirred for 1 hour. The solution was added with the compound (2.32 g) obtained in Example

39-2 and the whole was stirred overnight at room temperature. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform, washed with a saturated aqueous ammonium chloride solution, a saturated aqueous sodium hydrogen carbonate solution, and a saturated saline solution, and then dried with anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (4.06 g) as a white solid.

MS(FAB,Pos.):m/z=333$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=1.34-1.46(2H,m),1.38(9H,s),1.56(2H,quint.,J=7.3Hz),2.33(2H,t,J=7.3Hz),2.93(2H,dt,J=6.1,6.8Hz),5.93(2H,br),6.76(1H,d,J=8.4Hz),6.83(1H,t,J=5.4Hz),7.28(1H,d,J=8.4Hz),7.61(1H,s),9.10(1H,s).

Example 45-4: Synthesis of 2-(4-dipropylamino-butyl)-3-(2-hydroxy-ethyl)-3H-benzinidazol-5-carbonitrile

The compound (175.1 mg) obtained in Example 45-3 was dissolved in DMF (4.0 ml). The reaction solution was cooled to 0°C and added with 60% sodium hydride (45.2 mg) and the whole was stirred at room temperature for 40 minutes. Then, the compound (179.9 mg) obtained in Example 45-1 was added thereto and the whole was stirred at room temperature for 2 hours. The reaction solution was added with distilled water and subjected to extraction with diethylether. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The drying agent was filtrated out and then the organic layer was

concentrated under reduced pressure.

The resultant was dissolved in methanol (3.0 ml). The reaction solution was added with a 4 mol/l hydrogen chloride/dioxane solution (2.0 ml) and the whole was stirred at room temperature for 1.5 hours. The reaction solution was concentrated under reduced pressure and added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The drying agent was filtrated out and then the organic layer was concentrated under reduced pressure.

The resultant was dissolved in methanol (1.5 ml). The reaction solution was added with trimethyl orthoformate (76 µl) and the whole was cooled to 0°C. After that, a methanol solution (1.0 ml) in which propionaldehyde (40.1 mg) was dissolved was dropped thereto and the whole was stirred at room temperature for 20 minutes. Subsequently, the solution was added with sodium cyanoborohydride (43.7 mg) and the whole was stirred at room temperature for 14.5 hours. The reaction solution was concentrated under reduced pressure and added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The drying agent was filtrated out and then the organic layer was concentrated under reduced pressure. The resultant residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (41.8 mg) as a purple solid.

MS(FAB,Pos.):m/z=343$[M+H]^+$

Example 45-5: Synthesis of 2-(2-(4-dipropylamino-butyl)-6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzimidazol-1-yl)-ethanol [Compound No. 45]

The compound (41.8 mg) obtained in Example 45-4 was dissolved in ethanol (1.5 ml). The reaction solution was added with a 1 mol/l sodium hydroxide aqueous solution (0.3 ml) and Raney nickel (4.3 mg). The whole was stirred at room temperature for 17 hours under a hydrogen atmosphere. Then, the resultant was filtrated through Celite and added with distilled water, followed by extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The drying agent was filtrated out and then the organic layer was concentrated under reduced pressure.

The resultant was dissolved in methanol (1.2 ml). The reaction solution was added with 2-imidazole carboxaldehyde (11.0 mg) and trimethyl orthoformate (30 μl) and the whole was stirred at room temperature for 1.5 hours. After having been cooled to 0°C, the reaction solution was added with sodium borohydride (2.7 mg) and the whole was stirred at room temperature for 1.5 hours. The reaction solution was concentrated under reduced pressure and added with distilled water, and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The drying agent was filtrated out and then the organic layer was concentrated under reduced pressure.

The resultant was dissolved in methanol (1.0 ml) and added with 1-methyl-2-imidazole carboxaldehyde (14.8 mg) and sodium

cyanoborohydride (15.4 mg). The solution was adjusted to pH 5 with acetic acid and stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure. The resultant residue was added with a 1 mol/l sodium hydroxide aqueous solution and subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The drying agent was filtrated out and then the organic layer was concentrated under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (32.4 mg) of the subject compound as a pale-yellow solid.

MS(FAB,Pos.):m/z=522[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.91(6H,t,J=7.3Hz),1.65-1.73(4H,m),1.83(2H,m),1.93(2H,m),2.99(4H,br),3.11(2H,br),3.29(2H,br),3.73(3H,s),3.88(2H,s),4.12(2H,s),4.20(2H,s),4.66(2H,br),7.53-7.55(3H,m),7.64(2H,s),7.70(1H,d,J=8.2Hz),8.33(1H,d,J=8.2Hz),10.27(1H,br).

[Example 46]

[0109]

Production example 46: Synthesis of [3-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-propyl]-dipropyl-amine [Compound No. 46]

Example 46-1: Synthesis of 3,4-diaminobenzonitrile

An ethanol solution (300 ml) containing 4-amino-3-nitrobenzonitrile (3.00 g) was added with stannous chloride dihydrate (20.7 g) and then added with sodium borohydride

(348 mg). The whole was stirred overnight at 60°C. After that, the resultant was subjected to distillation until the amount of the solution became about 100 ml. The resultant was added with water (100 ml) and a large amount of solid component was generated.

The resultant was added with a 5 mol/l sodium hydroxide aqueous solution (42 ml) to adjust to pH 7. The solvent was distilled off. The solid component was filtrated out through Celite and washed with methanol and ethyl acetate in the stated order. The filtrate was again filtrated through Celite and only organic solvent was distilled off under reduced pressure. The remaining aqueous layer was subjected to extraction with ethyl acetate and dried with anhydrous magnesium sulfate, and the solvent was distilled off, thereby obtaining the subject compound (2.29 g) as a khaki crystal.

[0110]

Example 46-2: Synthesis of [3-(2-amino-5-cyano-phenylcarbamoyl)-propyl]-carbamic acid t-butyl ester

A DMF solution (30 ml) containing 4-(t-butoxycarbonylamino)-butyric acid (1.53 g) was added with HOBt (1.07 g) and WSCI hydrochloride (1.51 g) and the whole was stirred for 0.5 hours. The reaction solution was dropped to a DMF solution (12 ml) containing the compound (1.00 g) obtained in Example 46-1. The whole was stirred at room temperature for 12 hours and then the solvent was distilled off. The resultant was dissolved in chloroform, washed with a saturated aqueous ammonium chloride solution and a saturated aqueous sodium hydrogen carbonate solution in the stated order, and dried with anhydrous

magnesium sulfate. The residue obtained by distilling the solvent off was purified through silica gel column chromatography (ethyl acetate/chloroform), thereby obtaining the subject compound (1.57 g) as a milky-white solid.

MS(FAB,Pos.):m/z=319[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=1.38(9H,s),1.68(2H,quint.,J=7.1Hz),2.32(2H,t,J=7.6Hz),2.97(2H,q,J=6.6Hz),5.95(2H,s),6.75(1H,d,J=8.5Hz),6.86(1H,t,J=5.6Hz),7.28(1H,dd,J=2.2,8.5Hz),7.59(1H,d,J=1.7Hz),9.08(1H,s).

Example 46-3: Synthesis of {3-[(2-amino-5-cyano-phenyl)-propyl-carbamoyl]-propyl}-carbamic acid t-butyl ester

A DMF solution (4.0 ml) containing the compound (0.501 g) obtained in Example 46-2 was added with 60% sodium hydride (76.0 mg) and the whole was stirred at room temperature for 30 minutes. The solution was cooled with ice and then 1-iodopropane (0.184 ml) was dropped thereto. The whole was stirred at room temperature for 23 hours. The solvent in the reaction solution was distillated off. The resultant was dissolved in chloroform, washed with a saturated aqueous sodium hydrogen carbonate solution, and dried with anhydrous magnesium sulfate. The residue obtained by distilling the solvent off was purified through silica gel column chromatography (ethyl acetate/chloroform), thereby obtaining the subject compound (0.378 g) as a colorless crystal.

MS(FAB,Pos.):m/z=343[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.99(3H,t,J=7.3Hz),1.42(9H,s),1.85(2H,sext.,J=7.3Hz),2.14(2H,quint.,J=7.3Hz),2.95(2H,t,J=7.3Hz),3.30(2H,q,J=6.3Hz),4.10(2H,t,J=7.3Hz),4.86(1H,br),7.50(1H,dd,J

=1.5,8.3Hz),7.64(1H,dd,J=0.7,1.5Hz),7.75(1H,dd,J=0.5,8.3Hz).

Example 46-4: Synthesis of 2-(3-aminopropyl)-3-propyl-3H-benzo[d]imidazol-5-carbonitrile

The compound (0.375 g) obtained in Example 46-3 was dissolved in ethyl acetate (4.0 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (1.09 ml). The whole was stirred for 20 minutes and added with methanol (8.0 ml), followed by distillating off the solvent. The concentrate was added with chloroform and washed with a 1 mol/l sodium hydroxide aqueous solution, and the aqueous layer was extracted with chloroform. The organic layer was dried with anhydrous sodium sulfate and the solvent was distilled off, thereby obtaining a crude product (0.314 g) containing the subject compound as an amber liquid.

[0111]

Example 46-5: Synthesis of 2-(3-(dipropylamino)propyl)-3-propyl-3H-benzo[d]imidazol-5-carbonitrile

A methanol solution (8.0 ml) containing the crude product (0.314 g) of the compound obtained in Example 46-4 was added with acetic acid (100 µl) and added with sodium cyanoborohydride (0.275 g). Propionaldehyde (0.237 ml) was gradually dropped thereto. After the whole was stirred at room temperature for 13 hours, the solvent was distilled off. The resultant was added with ethyl acetate, washed with a saturated aqueous sodium hydrogen carbonate solution, and dried with anhydrous magnesium sulfate. The residue obtained by filtration and distilling the solvent off

was purified through silica gel column chromatography (methanol/chloroform), thereby obtaining the subject compound (0.365 g) as a pale-yellow oily substance.

MS(FAB,Pos.):m/z=327[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.92(6H,t,J=7.3Hz),1.00(3H,t,J=7.3Hz),1.54(4H,sext.,J=7.6Hz),1.86(2H,sext.,J=7.3Hz),2.17(2H,quint.,J=6.3Hz),2.58(4H,br),2.79(2H,br),3.01(2H,t,J=7.3Hz),4.13(2H,t,J=7.3Hz),7.50(1H,dd,J=1.5,8.3Hz),7.65(1H,dd,J=0.7,1.5Hz),7.73(1H,dd,J=0.7,8.3Hz).

Example 46-6: Synthesis of 3-[6-(aminomethyl)-1-propyl-1H-benzo[d]imidazol-2-yl]-N,N-dipropylpropan-1-amine

An ethanol solution (12 ml) containing the compound (0.363 g) obtained in Example 46-5 was added with a 1 mol/l sodium hydroxide aqueous solution (3.6 ml) and added with Raney nickel (120 mg). The whole was stirred for 6 hours under a hydrogen atmosphere. The catalyst was removed by filtration through Celite and the solvent was distilled off. After that, the resultant was partitioned into chloroform and water. The solution was washed with a saturated aqueous sodium hydrogen carbonate solution, and dried with anhydrous magnesium sulfate. The residue obtained by distilling the solvent off was purified through silica gel column chromatography (chloroform), thereby obtaining the subject compound (0.244 g) as a colorless liquid.

MS(FAB,Pos.):m/z=331[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.3Hz),0.99(3H,t,J=7.6Hz),1.44(4H,sext.,J=7.3Hz),1.60(2H,br),1.84(2H,sext.,J=7.6Hz),2.04(2H,quint.,J=7.8Hz),2.39(4H,t,J=7.8Hz),2.56(2H,t,J=6.8Hz),

2.88(2H,t,J=7.6Hz),4.00(2H,s),4.08(2H,t,J=7.3Hz),7.15(1H,dd,J=1.7,8.3Hz),7.28(1H,d,J=1.0Hz),7.66(1H,d,J=8.3Hz).

Example 46-7: Synthesis of 3-(6-{[(1H-imidazol-2-yl)methylamino]methyl}-1-propyl-1H-benzo[d]imidazol-2-yl)-N,N-dipropylpropan-1-amine

An anhydrous methanol solution (4.0 ml) containing the compound (0.244 g) obtained in Example 46-6 and 2-imidazole carboxaldehyde (85.0 mg) was added with trimethyl orthoformate (0.242 ml). The whole was stirred at room temperature for 14 hours and then added with sodium borohydride (0.140 g). After the solution was stirred for 2 hours, the solvent was distilled off. The resultant was dissolved in chloroform, washed with a saturated aqueous sodium hydrogen carbonate solution, and dried with anhydrous magnesium sulfate. The residue obtained by distilling the solvent off was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (0.167 g) as a colorless oily substance.

MS(FAB,Pos.):m/z=411$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.87(6H,t,J=7.3Hz),0.98(3H,t,J=7.6Hz),1.45(4H,sext.,J=7.6Hz),1.6-2.0(1H,br),1.83(2H,sext.,J=6.6Hz),2.04(2H,quint.,J=7.6Hz),2.40(4H,t,J=7.3Hz),2.57(2H,t,J=7.1Hz),2.88(2H,t,J=7.6Hz),3.93(2H,s),3.97(2H,s),4.07(2H,t,J=7.6Hz),6.99(2H,s),7.17(1H,d,J=8.3Hz),7.23(1H,s),7.65(1H,d,J=8.3Hz).

Example 46-8: Synthesis of [3-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-propyl]

-dipropyl-amine [Compound No. 46]

An anhydrous methanol solution (3.0 ml) containing the compound (0.166 g) obtained in Example 46-7 and 1-methyl-2-imidazole carboxaldehyde (53.0 mg) was added with 10 drops of acetic acid. The whole was added with sodium cyanoborohydride (76.0 mg) and stirred for 21 hours. After the solvent in the reaction solution was distillated off, the resultant was dissolved in chloroform, washed with a saturated aqueous sodium hydrogen carbonate solution, and dried with anhydrous magnesium sulfate. The residue obtained by distilling the solvent off was purified through silica gel column chromatography (chloroform), thereby obtaining the subject compound (86.0 mg) as a pale-yellow oily substance. The subject compound was treated with hydrochloric acid, thereby obtaining a hydrochloride (87.0 mg) of the subject compound as a colorless solid.

MS(FAB,Pos.):m/z=505$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.87(6H,t,J=7.3Hz),0.97(3H,t,J=7.3Hz),1.44(4H,sext.,J=7.6Hz),1.81(2H,sext.,J=7.6Hz),2.03(2H,quint.,J=7.6Hz),2.38(4H,t,J=7.6Hz),2.56(2H,t,J=6.8Hz),2.88(2H,t,J=7.6Hz),3.43(2H,s),3.50(3H,s),3.69(2H,s),3.82(2H,s),4.06(2H,t,J=7.3Hz),6.86(1H,d,J=1.5Hz),7.00(1H,d,J=1.2Hz),7.10(1H,s),7.15(1H,s),7.28(1H,s),7.33(1H,d,J=8.3Hz),7.67(1H,d,J=8.1Hz),12.4(1H,br).

[Example 47]

[0112]

Production example 47: Synthesis of [4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylm

ethyl)-amino]-methyl}-1-isopropyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 47]

Example 47-1: Synthesis of {4-[(2-amino-5-cyano-phenyl)-isopropyl-carbamoyl]-butyl}-carbamic acid t-butyl ester

The compound (242 mg) obtained in Example 45-3 was dissolved in DMF (5.0 ml). The solution was added with 60% sodium hydride (29.1 mg) and then 2-iodopropane (79.6 μl) in an ice bath. The whole was stirred overnight at room temperature. After completion of the reaction, the solvent was distilled off. The resultant was dissolved in chloroform and added with distilled water and the whole was stirred for a while. The solution was subjected to extraction with chloroform and washed with a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (44.1 mg) as a pale-yellow oily substance.

MS(FAB,Pos.):m/z=375$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=1.00(3H,d,J=6.6Hz),1.21(3H,d,J=6.6Hz),1.43(9H,s),1.53-1.65(4H,m),1.88-2.01(2H,m),3.00-3.07(2H,m),4.45(2H,brs),4.58(1H,brs),4.90(1H,sept.,J=6.6Hz),6.80(1H,d,J=8.3Hz),7.23(1H,d,J=2.0Hz),7.45(1H,dd,J=2.0,8.3Hz).

Example 47-2: Synthesis of 2-(4-amino-butyl)-3-isopropyl-3H-benzimidazol-5-carbonitrile

The compound (44.1 mg) obtained in Example 47-1 was dissolved in anhydrous methanol (1.0 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (1.0 ml) and the whole was stirred at

room temperature for 3 hours. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform and washed with a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (26.0 mg) as a white crystal.

MS(FAB,Pos.):m/z=257$[M+H]^+$

Example 47-3: Synthesis of 2-(4-dipropylamino-butyl)-3-isopropyl-3H-benzimidazol-5-carbonitrile

The compound (26.0 mg) obtained in Example 47-2 was dissolved in anhydrous methanol (1.0 ml) and added with sodium cyanoborohydride (19.1 mg), trimethyl orthoformate (27.7 μl), and propionaldehyde (18.3 μl). The whole was stirred overnight at room temperature under a nitrogen atmosphere. After completion of the reaction, the solvent was distilled off. The resultant was dissolved in chloroform and added with a saturated aqueous sodium hydrogen carbonate solution and the whole was stirred for a while. The resultant was subjected to extraction with chloroform and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (34.0 mg) as a pale-yellow oily substance.

MS(FAB,Pos.):m/z=341$[M+H]^+$

Example 47-4: Synthesis of

[4-(6-aminomethyl-1-isopropyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine

The compound (34.0 mg) obtained in Example 47-3 was dissolved in ethanol (2.0 ml) and added with a 1 mol/l sodium hydroxide aqueous solution (340 µl) and Raney nickel (4.0 mg). The whole was stirred overnight at room temperature under a hydrogen atmosphere. After completion of the reaction, the solution was filtrated through Celite and the solvent was distilled off. The resultant was subjected to extraction with chloroform and washed with a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (31.3 mg) as a pale-yellow oily substance.

MS(FAB,Pos.):m/z=345$[M+H]^+$

Example 47-5: Synthesis of N-[4-({[(1H-imidazol-2-yl)methyl]amino}methyl)benzyl]-N-(1-cyanoethyl)-N',N'-dipropylbutane-1,4-diamine

The compound (31.3 mg) obtained in Example 47-4 was dissolved in anhydrous methanol (1.0 ml) and added with trimethyl orthoformate (14.9 µl) and 2-imidazole carboxaldehyde (9.60 mg). The whole was stirred at room temperature for 2 hours under a nitrogen atmosphere. Subsequently, the solution was added with sodium borohydride (3.40 mg) in an ice bath and the whole was stirred at room temperature for 2 hours.

After completion of the reaction, the resultant was added with distilled water and the whole was stirred for a while. The resultant was subjected to extraction with chloroform and washed with a saturated aqueous sodium hydrogen carbonate solution and

a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (41.7 mg) as a colorless solid.
MS(FAB,Pos.):m/z=425$[M+H]^+$

Example 47-6: Synthesis of
[4-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-isopropyl-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 47]

The compound (41.7 mg) obtained in Example 47-5 was dissolved in anhydrous methanol (1.0 ml) and added with sodium cyanoborohydride (9.30 mg), acetic acid (100 µl), and 1-methyl-2-imidazole carboxaldehyde (11.9 mg). The whole was stirred overnight at room temperature under a nitrogen atmosphere. After completion of the reaction, the solvent was distilled off. The resultant was dissolved in chloroform and added with a 1 mol/l sodium hydroxide aqueous solution and the whole was stirred for a while. The resultant was subjected to extraction with chloroform and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution. The organic layer was dried with anhydrous sodium sulfate. The solvent was distilled off and the residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (26.4 mg) of the subject compound as a white solid.
MS(FAB,Pos.):m/z=519$[M+H]^+$
^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.3Hz),1.43-1.45(4H,m),1.63(6H,d,J=6.8Hz),1.62-1.65(2H,m),1.80-1.87(2H,m),2.36(4H,br),2.48(2H,br),2.90(3H,t,J=7.8Hz),3.43(2H,s),3.51(3H,s),3.70(2H

,s),3.82(2H,s),4.67(1H,sept.,J=6.8Hz),6.86(1H,d,J=1.2Hz),7.0
0(1H,d,J=1.2Hz),7.13(2H,d,J=22.2Hz),7.31(1H,dd,J=1.5,8.3Hz),
7.48(1H,s),7.66(1H,dd,J=3.9,8.3Hz),12.4(1H,br).

[Example 48]

[0113]

Production example 48: Synthesis of
[5-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylm
ethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-pentyl]
-dipropyl-amine [Compound No. 48]

Example 48-1: Synthesis of
[5-(2-amino-5-cyano-phenylcarbamoyl)-pentyl]-carbamic
acid-benzyl ester

The compound (510 mg) obtained in Example 46-1 was dissolved in DMF (20 ml). To this solution, a solution which was previously prepared by dissolving 6-benzyloxycarbonylamino-hexanoic acid (1.10 g) in DMF (10 ml), adding thereto WSCI hydrochloride (1.08 g) and HOBt (762 mg), and stirring the mixture for 30 minutes was dropped. The whole was stirred for 20 hours. The residue obtained by distilling the solvent off was subjected to extraction with chloroform. The organic layer was washed with water and a saturated saline solution, and dried with anhydrous sodium sulfate. The residue obtained by distilling the solvent off was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (961 mg) as a white solid.

MS(FAB,Pos.):m/z=381$[M+H]^+$

^{1}H-NMR(500MHz,DMSO):δ=1.30(2H,m),1.43(2H,tt,J=7.1,7.3Hz),1.5
8(2H,m),2.32(2H,t,J=7.4Hz),2.99(2H,dt,J=6.3,6.8Hz),5.00(2H,s

),5.93(2H,s),6.75(1H,d,J=8.3Hz),7.26-7.38(6H,m),7.62(1H,d,J=2.0Hz),9.08(1H,s).

Example 48-2: Synthesis of {5-[(2-amino-5-cyano-phenyl)-propyl-carbamoyl]-pentyl}-carbamic acid-benzyl ester

The compound (961 mg) obtained in Example 48-1 was dissolved in DMF (20 ml). After having been cooled to 0°C, the solution was added with 60% sodium hydride (72.9 mg) and warmed back to room temperature and the whole was stirred for 30 minutes. 1-Iodopropane (0.30 ml) was dropped to the solution and the whole was stirred for additional 3 hours. After having been cooled to 0°C, the solution was added with water to stop the reaction and concentrated. The residue was subjected to extraction with chloroform. The organic layer was washed with water and a saturated saline solution, and dried with anhydrous sodium sulfate. The residue obtained by distilling the solvent off was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (317 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=423$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.90(3H,t,J=7.3Hz),1.22-1.27(2H,m),1.40-1.46(2H,m),1.49-1.63(2H,m),1.89-1.94(1H,m),2.01-2.07(1H,m),3.10-3.17(3H,m),3.86-3.92(1H,m),4.40(2H,s),4.79(1H,s),5.08(2H,d,J=1.5Hz),6.76(1H,d,J=8.5Hz),7.25(1H,d,J=1.7Hz),7.30-7.38(5H,m),7.41(1H,dd,J=1.7,8.5Hz).

Example 48-3: Synthesis of [5-(6-cyano-1-propyl-1H-benzimidazol-2-yl)-pentyl]-carbamic

acid-benzyl ester

The compound (317 mg) obtained in Example 48-2 was dissolved in methanol (5.0 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (2.0 ml) and the whole was stirred for 16 hours. The residue obtained by distilling the solvent off was dissolved in methanol and the solution was neutralized with an anion-exchange resin (Amberlite IRA-410). The resin was filtrated out and the solvent was distilled off, thereby obtaining the subject compound (291 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=405[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.99(3H,t,J=7.3Hz),1.48-1.54(2H,m),1.58-1.62(2H,m),1.84(2H,tq,J=7.3,7.6Hz),1.95(2H,tt,J=7.3,7.6Hz),2.89(2H,t,J=7.6Hz),3.27(2H,d,J=7.6Hz),4.09(2H,t,J=7.4Hz),5.09(2H,s),5.15(1H,s),7.32-7.50(5H,m),7.62(1H,t,J=0.7Hz),7.72(1H,d,J=8.3Hz).

Example 48-4: Synthesis of
2-(5-amino-pentyl)-3-propyl-3H-benzimidazol-5-carbonitrile

The compound (107 mg) obtained in Example 48-3 was dissolved in ethanol (10 ml) and added with palladium carbon (20 mg) and the whole was stirred for 20 hours under a hydrogen atmosphere. After filtration through Celite, the solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (25.6 mg) as a white solid.

MS(FAB,Pos.):m/z=271[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=1.00(3H,t,J=7.4Hz),1.48-1.58(4H,m),1.82-1.89(2H,m),1.93-1.99(2H,m),2.73(2H,t,J=6.7Hz),2.90(2H,t,J=7.8Hz),4.10(2H,t,J=7.4Hz),7.49(1H,dd,J=1.7,8.3Hz),7.64(1H,dd

,J=0.7,1.5Hz),7.76(1H,dd,J=0.5,8.3Hz).

Example 48-5: Synthesis of 2-(5-dipropylamino-pentyl)-3-propyl-3H-benzimidazol-5-carbonitrile

The compound (26.4 mg) obtained in Example 48-4 was dissolved in methanol (2.0 ml) and added with sodium cyanoborohydride (15.8 mg). After the solution was adjusted to pH 4 with acetic acid, propionaldehyde (0.020 ml) was added thereto and the whole was stirred at room temperature for 20 hours. After the solvent was distilled off, the resultant was neutralized with a saturated aqueous sodium hydrogen carbonate solution and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining the subject compound (29.4 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=355$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.4Hz),1.00(3H,t,J=7.3Hz),1.40-1.49(6H,m),1.51-1.56(2H,m),1.81-1.88(2H,m),1.91-1.97(2H,m),2.36(4H,t,J=7.7Hz),2.41-2.44(2H,m),2.89(2H,t,J=7.9Hz),4.10(2H,t,J=7.4Hz),7.48(1H,dd,J=1.7,8.3Hz),7.63(1H,dd,J=1.5Hz),7.76(1H,dd,J=0.5,8.3Hz).

Example 48-6: Synthesis of [5-(6-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-pentyl]-dipropyl-amine

The compound (29.8 mg) obtained in Example 48-5 was dissolved in ethanol (20 ml) and added with a 1 mol/l sodium hydroxide aqueous

solution (4.0 ml). The solution was added with an ethanol suspension containing Raney nickel and the whole was stirred for 6 hours under a hydrogen atmosphere. After filtration through Celite, the solvent was distilled off and the resultant was subjected to extraction with chloroform.

The organic layer was washed with water and a saturated saline solution and then dried with anhydrous sodium sulfate. The solvent was distilled off.

The resultant was dissolved in methanol (2.0 ml) and added with 2-imidazole carboxaldehyde (13.4 mg) and trimethyl orthoformate (0.030 ml) and the whole was stirred at room temperature for 3 hours. After having been cooled to 0°C, the solution was added with sodium borohydride (10.5 mg) and warmed back to room temperature. The whole was stirred for 1 hour and added with water to stop the reaction. After that, the solvent was distilled off and the resultant was subjected to extraction with chloroform. The organic layer was washed with water and a saturated saline solution, and dried with anhydrous sodium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (26.0 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=439$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.87(3H,t,J=7.4Hz),1.01(6H,t,J=7.1Hz),1.40-1.49(4H,m),1.50-1.56(4H,m),1.78-1.86(2H,m),1.89-1.95(2H,m),2.25-2.38(2H,m),2.42(2H,t,J=7.4Hz),2.52(2H,q,J=7.1Hz),2.85(2H,t,J=7.8Hz),3.92(2H,s),3.96(2H,s),4.04(2H,t,J=7.4Hz),6.99(2H,s),7.15(1H,d,J=8.3Hz),7.22(1H,s),7.64(1H,d,J=8.1Hz).

Example 48-7: Synthesis of [5-(6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1-propyl-1H-benzimidazol-2-yl)-pentyl]-dipropyl-amine [Compound No. 48]

The compound (8.8 mg) obtained in Example 48-6 was dissolved in methanol (2.0 ml) and added with 1-methyl-2-imidazole carboxaldehyde (2.6 mg) and sodium cyanoborohydride (2.5 mg). After the solution was adjusted to pH 4 with acetic acid, the whole was stirred at room temperature for 18 hours. After the solvent was distilled off, the resultant was neutralized with a saturated aqueous sodium hydrogen carbonate solution and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and dried with anhydrous sodium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (9.3 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=533$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.90(6H,t,J=7.3Hz),0.99(3H,t,J=7.3Hz),1.41-1.44(2H,m),1.65-1.70(4H,m),1.76-1.80(4H,m),1.90(2H,m),2.96-3.06(6H,m),3.22(2H,m),3.73(3H,s),3.89(2H,s),4.12(2H,s),4.19(2H,s),4.53(2H,s),7.53(1H,s),7.55(2H,s),7.64(2H,s),7.69(1H,d,J=8.4Hz),8.41(1H,s),14.99(1H,br).

[Example 49]

[0114]

Production example 49: Synthesis of N-(4-{[(1H-imidazol-2-ylmethyl)-(5,6,7,8-tetrahydrohydro-qui

nolin-8-yl)-amino]-methyl}-benzyl)-N-methyl-N',N'-dipropyl-butane-1,4-diamine [Compound No. 49]

Example 49-1: Synthesis of N-(4-{[(1H-imidazol-2-ylmethyl)-(5,6,7,8-tetrahydrohydro-quinolin-8-yl)-amino]-methyl}-benzyl)-N-methyl-N',N'-dipropyl-butane-1,4-diamine [Compound No. 49]

The compound (203.5 mg) obtained in Example 9-2 was dissolved in anhydrous methanol (8.1 ml) and added with 6,7-dihydro-5H-quinolin-8-one (117.7 mg) which was synthesized by a known method and sodium cyanoborohydride (99.9 mg). After the solution was adjusted to pH 5 with acetic acid, the whole was stirred at room temperature for 2 days. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform. The resultant was dried with magnesium sulfate and the solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (69.5 mg) of the subject compound as a pale-yellow solid.

MS(FAB,Pos.):m/z=517$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6+D_2O):δ=0.92(6H,t,J=7.3Hz),1.63-1.76(6H,m),1.78-1.84(4H,m),1.92-1.98(4H,m),2.57(3H,s),2.98-3.07(10H,m),3.83(2H,s),4.10-4.16(2H,m),4.29-4.31(2H,m),4.50(1H,m),7.41(2H,d,J=7.8Hz),7.49(2H.s),7.55(2H,t,J=7.0Hz)8.39(2H,d,J=1.4Hz),8.83(1H,d,J=5.6Hz).

[Example 50]

[0115]

Production example 50: Synthesis of N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(5,6,7,8-tetrahydro-quinolin-8-yl)-amino]-methyl}-benzyl)-methanesulfonamide [Compound No. 50]

Example 50-1: Synthesis of (4-{[(4-dipropylamino-butyl)-methanesulfonyl-amino]-methyl}-benzyl)-carbamic acid t-butyl ester

The compound (198.3 mg) obtained in Example 23-4 was dissolved in anhydrous dichloromethane (4.0 ml) and added with triethylamine (0.142 ml) and methanesulfonyl chloride (0.060 ml), and the whole was stirred at room temperature for 1 hour. After completion of the reaction, the resultant was washed with water and dried with anhydrous magnesium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (192.0 mg) as a colorless oily substance.
MS(FAB,Pos.):m/z=469$[M+H]^+$

Example 50-2: Synthesis of N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-methanesulfonamide

The compound (192 mg) obtained in Example 50-1 was dissolved in methanol (2.0 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (2.0 ml) and the whole was stirred at room temperature for 1 hour. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform. The resultant was dried with magnesium sulfate and the solvent was distilled off.

The resultant was dissolved in anhydrous methanol (7.0 ml) and added with 2-imidazole carboxaldehyde (59.6 mg) and trimethyl orthoformate (0.135 ml) and the whole was stirred at room temperature for 14.5 hours. The solution was added with sodium borohydride (46.5 mg) and the whole was stirred at room temperature for 30 minutes. After completion of the reaction, the solvent was distilled off. The resultant was added with water and subjected to extraction with chloroform. The resultant was dried with magnesium sulfate and the solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (154 mg) as a colorless oily substance.

MS(FAB,Pos.):m/z=450$[M+H]^+$

Example 50-3: Synthesis of N-(4-dipropylamino-butyl)-N-(4-{[(1H-imidazol-2-ylmethyl)-(5,6,7,8-tetrahydro-quinolin-8-yl)-amino]-methyl}-benzyl)-methanesulfonamide [Compound No. 50]

The compound (154 mg) obtained in Example 50-2 was dissolved in anhydrous methanol (6.2 ml) and added with 6,7-dihydro-5H-quinolin-8-one (75.1 mg) which was synthesized by a known method and sodium cyanoborohydride (64.1 mg). After the solution was adjusted to pH 5 with acetic acid, the whole was stirred at room temperature for 2 days. After completion of the reaction, the solvent was distilled off. The resultant was added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform. The resultant was dried with magnesium sulfate and the solvent was distilled off. The residue was purified through silica gel column

chromatography (chloroform/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (69 mg) of the subject compound as a pale-yellow solid.

MS(FAB,Pos.):m/z=581[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.87(6H,t,J=7.3Hz),1.40-1.52(4H,m),1.59-1.66(4H,m),2.10-2.15(4H,m),2.87-2.90(6H,m),2.96(3H,s),3.05-3.08(4H,m),4.11(2H,d,J=15.5Hz),4.24(2H,s),4.29-4.43(1H,m),4.92(2H,brs),7.21(2H,d,J=7.8Hz),7.56(2H,s),7.90(1H,t,J=6.1Hz),8.20(2H,d,J=7.6Hz),8.36(1H,t,J=6.3Hz),8.86(1H,d,J=5.3Hz).

[Example 51]

[0116]

Production example 51: Synthesis of 3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid [Compound No. 51]

Example 51-1: Synthesis of 3-[(4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-propionic acid [Compound No. 51]

The compound (129 mg) obtained in Example 34-3 was dissolved in anhydrous methanol (1.0 ml) and added with concentrated hydrochloric acid (10.0 ml) and the whole was refluxed under heating. After completion of the reaction, the solvent was distilled off, thereby obtaining a hydrochloride (71.4 mg) of the subject compound as a pale-yellow solid.

MS(FAB,Pos.):m/z=538[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6+D_2O):δ=0.92(6H,t,J=7.5Hz),1.63-1.69(6H,m),1.79(2H,br),2.85-3.08(10H,m),3.16-3.22(2H,m),3.64(2H,s),3

.75(3H,s),4.11(2H,s),4.19(2H,s),4.27-4.37(2H,m),7.31(2H,d,J=8.1Hz),7.46-7.51(3H,m),7.60(2H,s),7.56-7.63(1H,m).

[Example 52]

[0117]

Production example 52: Synthesis of (4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-cyanamide

[Compound No. 52]

Example 52-1: Synthesis of (4-cyano-benzyl)-(4-dipropylamino-butyl)-carbamic acid t-butyl ester

The compound (236 mg) obtained in Example 1-2 was dissolved in methanol (4.0 ml) and added with trimethyl orthoformate (380 µl) and 4-cyanobenzaldehyde (159 mg) at room temperature and the whole was stirred at room temperature for 16 hours under a nitrogen atmosphere. After that, the solution was added with sodium borohydride (103 mg) under ice-cooling and the whole was stirred at room temperature for 30 minutes. After completion of the reaction, the solution was added with water and the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and added with water, and the aqueous layer was extracted with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining a yellow oily substance (384 mg). 293 mg of the substance was dissolved in chloroform (6.0 ml) and added with di-t-butyldicarbonate (334 mg) and the whole was stirred at room temperature for 10 hours under a nitrogen atmosphere. After completion of the reaction,

the resultant was added with a saturated sodium hydrogen carbonate aqueous solution (3.0 ml) and the aqueous layer was extracted with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The solvent was distilled off and the residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (331 mg) as a yellow oily substance.
MS(FAB,Pos.):m/z=388$[M+H]^+$

Example 52-2: Synthesis of (4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-carbamic acid t-butyl ester

The compound (331 mg) obtained in Example 52-1 was dissolved in ethanol (13 ml) and added with a 1 mol/l sodium hydroxide aqueous solution (3.0 ml) and an ethanol suspension containing Raney nickel and the whole was stirred for 3 hours at room temperature under a hydrogen atmosphere. After completion of the reaction, the solution was filtrated through Celite and the solvent was distilled off. The residue was dissolved in chloroform and the aqueous layer was extracted with chloroform. The organic layer was washed with a saturated saline solution and then dried with anhydrous sodium sulfate. The solvent was distilled off, thereby obtaining a colorless oily substance (283 mg).

The substance was dissolved in methanol (6.0 ml) and added with trimethyl orthoformate (240 µl) and 2-imidazole carboxaldehyde (83.7 mg) at room temperature and the whole was stirred at room temperature for 15 hours under a nitrogen atmosphere. After that, the solution was added with sodium

borohydride (59.0 mg) under ice-cooling and the whole was stirred for 30 minutes at room temperature. After completion of the reaction, the solution was added with water and the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and added with water, and then the aqueous layer was extracted with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The solvent was distilled off.

The resultant was dissolved in ethanol (7.0 ml) and added with 1-methyl-2-imidazole carboxaldehyde (117 mg) and sodium triacetoxyborohydride (326 mg) and the whole was stirred at room temperature for 17 hours under a nitrogen atmosphere. After completion of the reaction, a saturated aqueous sodium hydrogen carbonate solution (20 ml) was poured to the resultant and the solvent was distilled off. The residue was dissolved in chloroform and then the aqueous layer was extracted with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (360 mg) as a yellow oily substance.
MS(FAB,Pos.):m/z=566$[M+H]^+$

Example 52-3: Synthesis of
N-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-N',N'-dipropyl-butane-1,4-diamine

The compound (360 mg) obtained in Example 52-2 was dissolved in methanol (3.6 ml) and added with a 4 mol/l hydrogen

chloride/dioxane solution (3.6 ml) and the whole was stirred at room temperature for 13 hours under a nitrogen atmosphere. After completion of the reaction, the solvent was distilled off.

The residue was dissolved in chloroform and the aqueous layer was extracted with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (306 mg) as a pale-yellow oily substance.

MS(FAB,Pos.):m/z=465$[M+H]^+$

Production example 52-4: Synthesis of (4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-cyanamide [Compound No. 52]

The compound (13.4 mg) obtained in Example 52-3 was dissolved in THF (0.26 ml) and added with triethylamine (10 μl) and bromocyan (3.65 mg) and the whole was stirred at room temperature for 2 hours under a nitrogen atmosphere. After completion of the reaction, the solution was added with a saturated aqueous sodium hydrogen carbonate solution to neutralize the solution and the solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol) and treated with tartaric acid, thereby obtaining a tartrate (12.5 mg) of the subject compound as a white solid.

MS(FAB,Pos.):m/z=491$[M+H]^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.86(6H,t,J=7.4Hz),1.39-1.50(6H,m),1.67(2H,quint.,J=7.5Hz),2.30-2.34(4H,m),2.39(2H,t,J=7.3Hz),2.96

(2H,t,J=7.3Hz),3.48(2H,s),3.58(3H,s),3.60(2H,s),3.69(2H,s),4.17(2H,s),6.89(1H,d,J=1.2Hz),7.00(1H,d,J=1.2Hz),7.08(1H,brs),7.13(1H,brs),7.31(2H,d,J=8.1Hz),7.44(2H,d,J=8.1Hz),12.37(1H,brs).

[Example 53]

[0118]

Production example 53: Synthesis of (4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-formamide [Compound No. 53]

Example 53-1: Synthesis of (4-dipropylamino-butyl)-(4-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-formamide [Compound No. 53]

The compound (82.9 mg) obtained in Example 52-3 was dissolved in ethanol (1.0 ml) and added with formic acid (50 μl) and formamide (50 μl). The whole was stirred at an outside temperature of 100°C for 3 hours. The solution was added with additional formic acid (60 μl) and the whole was stirred for 15 hours. After completion of the reaction, the solvent was distilled off. The residue was dissolved in chloroform and added with a 1 mol/l sodium hydroxide aqueous solution to adjust the pH to 11. The aqueous layer was extracted with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The solvent was distilled off. The residue was purified through silica gel column chromatography (chloroform/methanol) and treated with hydrochloric acid, thereby obtaining a hydrochloride (27.0 mg) of the subject compound as a yellow solid.

MS(FAB,Pos.):m/z=494[M+H]$^+$

^{1}H-NMR(500MHz,$CDCl_3$):δ=0.85(6H,t,J=7.2Hz),1.23-1.56(6H,m),2.29-2.37(6H,m),3.14(2H,t,J=7.0Hz),3.23(2H,t,J=7.3Hz),3.46(2H,s),3.49(2H,s),3.57(2H,s),3.59(2H,s),3.60(3H,s),3.67(2H,s),3.68(2H,s),4.38(2H,s),4.53(2H,s),6.88(1H,d,J=1.2Hz),6.89(1H,d,J=1.4Hz),7.00(1H,d,J=1.2Hz),7.01(2H,d,J=1.2Hz),7.08(1H,s),7.13(1H,s),7.18(1H,d,J=8.3Hz),7.22(1H,d,J=8.0Hz),7.37(1H,d,J=8.0Hz),7.43(1H,d,J=8.3Hz),8.20(1H,s),8.28(1H,s),12.38(1H,brs).

[Example 54]

[0119]

Production example 54: Synthesis of [(4-{[(1-carboxymethyl-1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)amino]-acetic acid [Compound No. 54]

Example 54-1: Synthesis of [(4-dipropylamino-butyl)-(4-{[(1-methoxycarbonylmethyl-1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-amino]-acetic acid methyl ester

The compound (81.9 mg) obtained in Example 52-3 was dissolved in THF (2.0 ml) and added with triethylamine (76.0 µl) and methyl bromoacetate (46.0 µl) and the whole was stirred at room temperature for 11 hours under a nitrogen atmosphere. After completion of the reaction, the solution was added with methanol and the solvent was distilled off under reduced pressure. The residue was purified through silica gel column chromatography (chloroform/methanol), thereby obtaining the subject compound (23.7 mg) as a yellow oily substance.

MS(FAB,Pos.):m/z=610[M+H]$^+$

Example 54-2: Synthesis of [(4-{[(1-carboxymethyl-1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-benzyl)-(4-dipropylamino-butyl)amino]-acetic acid

The compound (23.7 mg) obtained in Example 54-1 was dissolved in 1,4-dioxane (1.0 ml) and added with concentrated hydrochloric acid (1.0 ml) and the whole was refluxed under heating for 4 hours. After completion of the reaction, the solvent was distilled off under reduced pressure, thereby obtaining a hydrochloride (17.2 mg) of the subject compound as a yellow solid.

MS(FAB,Pos.):m/z=582$[M+H]^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.90(6H,t,J=7.3Hz),1.66-1.80(8H,m),2.94-3.17(8H,m),3.38-3.83(5H,m),3.90(2H,brs),4.13(2H,brs),4.17(2H,brs),4.35(2H,brs),5.16(2H,brs),7.44(2H,d,J=8.3Hz),7.47(2H,d,J=8.0Hz),7.52(1H,s),7.55(1H,s),7.65(1H,s),7.66(1H,s).

[Example 55]

[0120]

Production example 55: Synthesis of [4-(1-benzyl-6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 55]

Example 55-1: Synthesis of 3-benzyl-2-(4-t-butoxycarbonylamino-butyl)-3H-benzimidazol-5-carboxylic acid methyl ester

The compound (965.3 mg) obtained in Example 2-1 was dissolved in DMF (20 ml). After having been cooled to 0°C, the reaction solution was added with 60% sodium hydride (221.8 mg) and the

whole was stirred at room temperature for 1 hour. After that, benzylbromide (0.35 ml) was added to the solution and the whole was stirred at room temperature for 3 hours. The reaction solution was concentrated under reduced pressure. The resultant residue was added with distilled water and subjected to extraction with ethyl acetate. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The drying agent was filtrated out and then the organic layer was concentrated under reduced pressure. The resultant residue was purified through silica gel column chromatography (chloroform/ethyl acetate), thereby obtaining the subject compound (0.469 g) as a white solid.

MS(FAB,Pos.):m/z=438$[M+H]^+$

Example 55-2: Synthesis of 3-benzyl-2-(4-dipropylamino-butyl)-3H-benzimidazol-5-carboxylic acid methyl ester

The compound (0.469 g) obtained in Example 55-1 was dissolved in methanol (5.0 ml) and added with a 4 mol/l hydrogen chloride/dioxane solution (3.0 ml) and the whole was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure. The resultant residue was added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The drying agent was filtrated out and then the organic layer was concentrated under reduced pressure.

The resultant was dissolved in methanol (8.0 ml). The reaction solution was added with trimethyl orthoformate (0.25

ml) and the whole was cooled to 0°C. After that, a solution which propionaldehyde (134.4 mg) was dissolved in methanol (1.0 ml) was dropped thereto and the whole was stirred at room temperature for 25 minutes. Subsequently, the solution was added with sodium cyanoborohydride (214 mg) and the whole was stirred at room temperature for 16 hours. The reaction solution was concentrated under reduced pressure and the resultant residue was added with a 1 mol/l sodium hydroxide aqueous solution. The whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The drying agent was filtrated out and then the organic layer was concentrated under reduced pressure. The resultant residue was purified through silica gel column chromatography (hexane/ethyl acetate), thereby obtaining the subject compound (267 mg) as a yellow oily substance.
MS(FAB,Pos.):m/z=422$[M+H]^+$

Example 55-3: Synthesis of 3-benzyl-2-(4-dipropylamino-butyl)-3H-benzimidazol-5-carbaldehyde

The compound (267 mg) obtained in Example 55-2 was dissolved in THF (5.0 ml). After having been cooled to 0°C, the reaction solution was added with Lithium aluminum hydride (38.5 mg) and the whole was stirred at room temperature for 40 minutes. After that, the solution was again cooled to 0°C. The reaction solution was added with acetone (1.0 ml) and ethyl acetate (2.0 ml) and the whole was stirred at room temperature for 20 minutes. Then, the reaction solution was added with a saturated aqueous sodium potassium tartrate solution and the whole was vigorously stirred

at room temperature for 19 hours. The reaction solution was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated saline solution and dried with an anhydrous sodium sulfate.

The drying agent was filtrated out and then the organic layer was concentrated under reduced pressure.

The resultant was dissolved in chloroform (5.0 ml). The reaction solution was added with manganese dioxide (1.14 g) and the whole was stirred at room temperature for 3 hours. The reaction solution was filtrated through Celite. The filtrate was concentrated under reduced pressure, thereby obtaining the subject compound (25.5 mg) as a yellow oily substance.
MS(FAB,Pos.):m/z=392$[M+H]^+$

Example 55-4: Synthesis of
[4-(1-benzyl-6-{[(1H-imidazol-2-ylmethyl)-(1-methyl-1H-imidazol-2-ylmethyl)-amino]-methyl}-1H-benzimidazol-2-yl)-butyl]-dipropyl-amine [Compound No. 55]

The compound (225 mg) obtained in Example 55-3 was dissolved in methanol (4.0 ml). The solution was added with the compound (64.5 mg) obtained in Example 14-7 and trimethyl orthoformate (0.13 ml) and the whole was stirred at room temperature for 1.5 hours. After having been cooled to 0°C, the reaction solution was added with sodium borohydride (20.8 mg) and the whole was stirred at room temperature for 20 minutes. After the reaction solution was concentrated under reduced pressure, the resultant residue was added with distilled water and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with an anhydrous sodium

sulfate. The drying agent was filtrated out and then the organic layer was concentrated under reduced pressure.

The resultant was dissolved in methanol (6.0 ml). The reaction solution was added with 2-imidazole carboxaldehyde (83.3 mg) and sodium cyanoborohydride (77.3 mg). The whole was added with acetic acid to adjust the pH to 5 and stirred at room temperature for 18 hours. The reaction solution was concentrated under reduced pressure. The resultant residue was added with a 1 mol/l sodium hydroxide aqueous solution and the whole was subjected to extraction with chloroform. The organic layer was washed with a saturated saline solution and dried with anhydrous sodium sulfate. The drying agent was filtrated out and then the organic layer was concentrated under reduced pressure. The resultant residue was purified through silica gel column chromatography (hexane/ethyl acetate) and treated with hydrochloric acid, thereby obtaining a hydrochloride (174.3 mg) of the subject compound as a white solid.

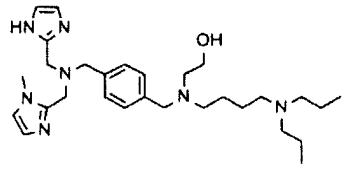
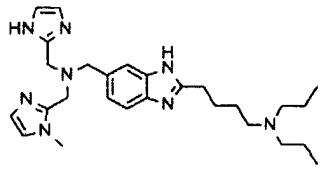
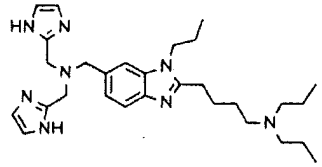
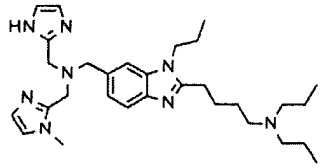
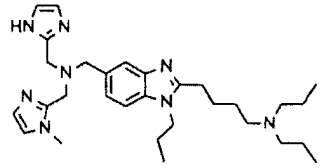
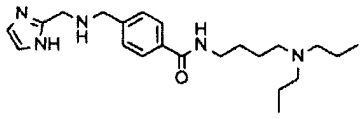
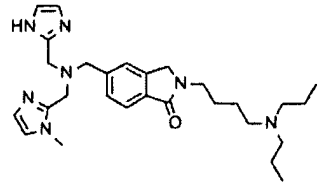
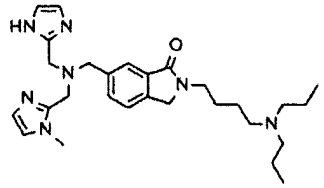
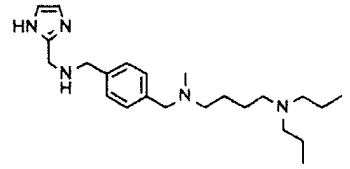
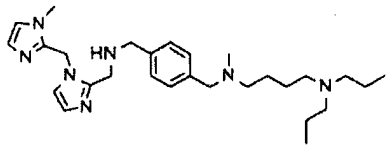
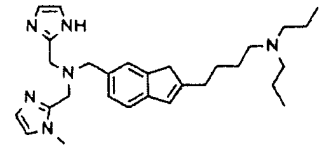
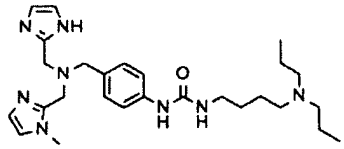
MS(FAB,Pos.):m/z=567[M+H]$^+$

^{1}H-NMR(500MHz,DMSO-d_6):δ=0.90(6H,t,J=7.3Hz),1.64-1.86(8H,m),2.95(4H,br),3.05(2H,br),3.28(2H,br),3.67(3H,s),3.83(2H,s),4.10(2H,s),4.17(2H,s),5.94(2H,s),7.31-7.39(5H,m),7.49-7.54(3H,m),7.60(2H,s),7.72(1H,d,J=8.4Hz),8.17(1H,s),10.43(1H,br),14.94(2H,br).

Next, the structural formulae of the compounds of the present invention including the compounds or the like produced in Production Examples described above are shown in Table 1.

[0121]

[Table 1]

No.	Structural Formula	No.	Structural Formula
1		2	
3		4	
5		6	
7		8	
9		10	
11		12	

[0122]

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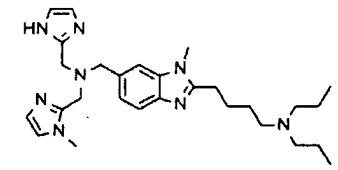
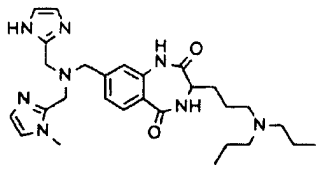
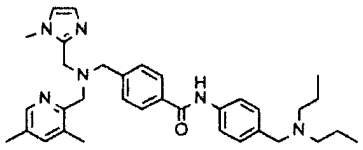
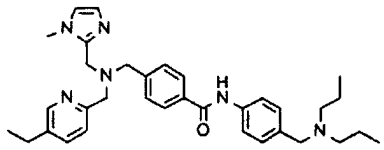
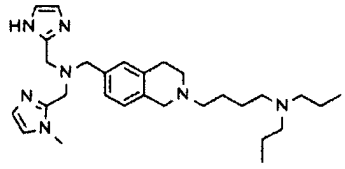
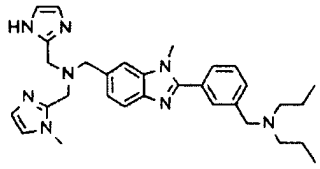
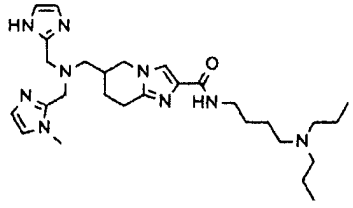
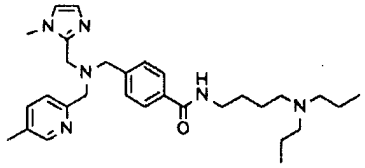
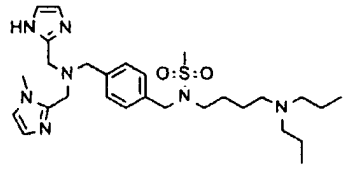
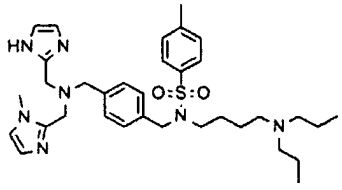
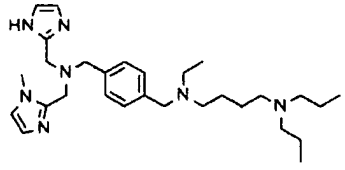
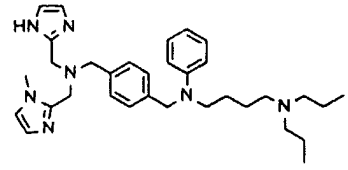
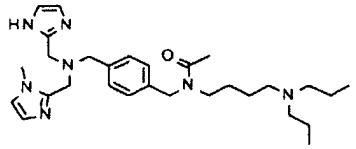
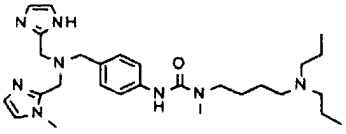
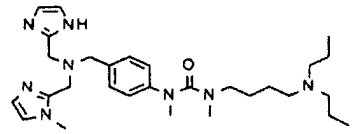
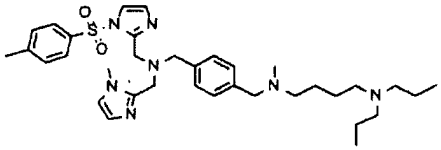
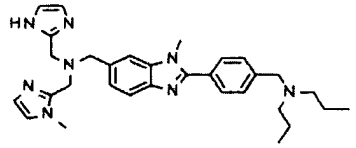
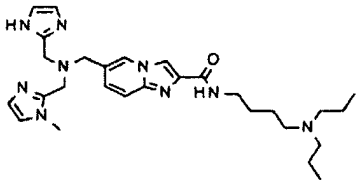
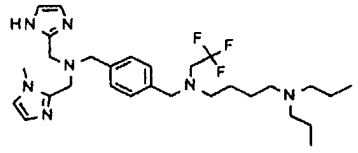
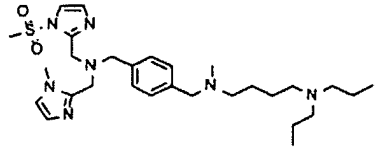
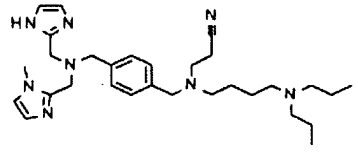
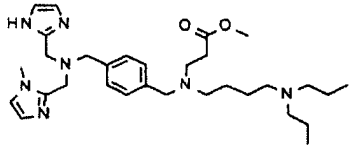
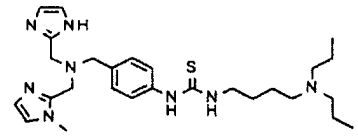
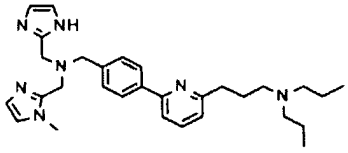
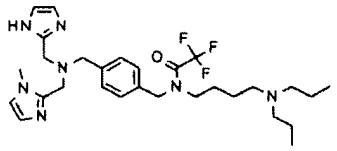
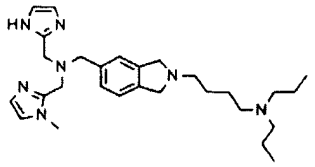
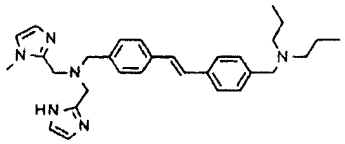
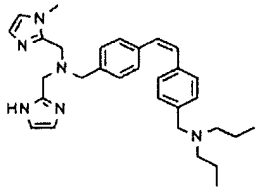
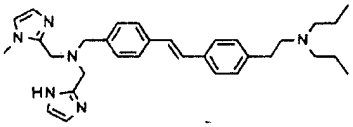
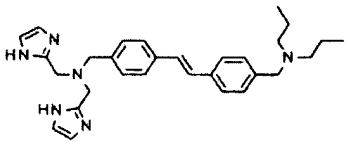
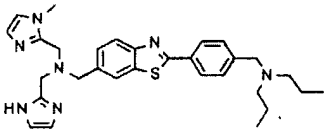
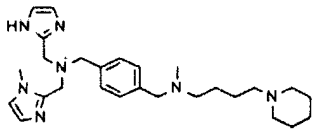
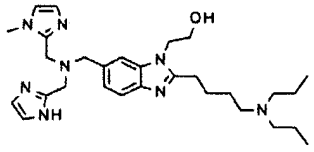
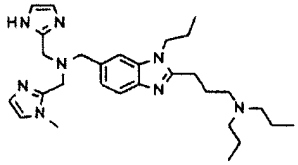
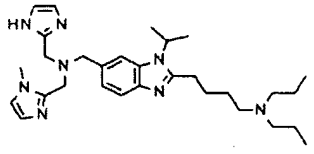
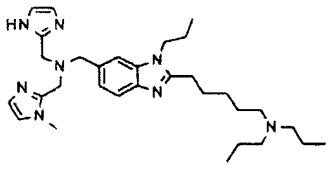
13		14	
15		16	
17		18	
19		20	
21		22	
23		24	

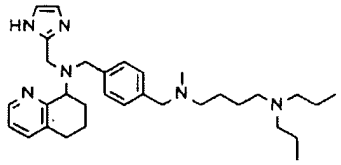
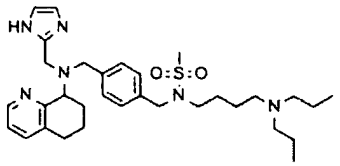
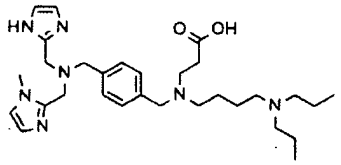
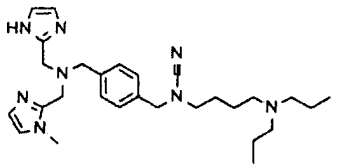
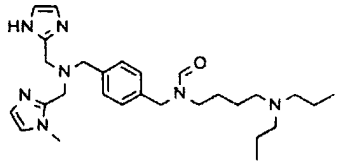
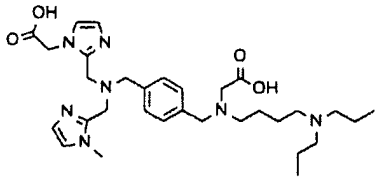
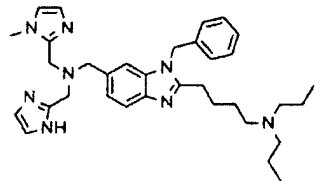
[0123]

No.	Structural Formula	No.	Structural Formula
25		26	
27		28	
29		30	
31		32	
33		34	
35		36	

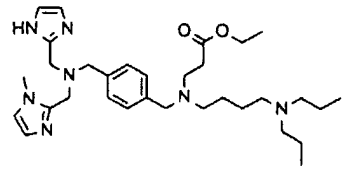
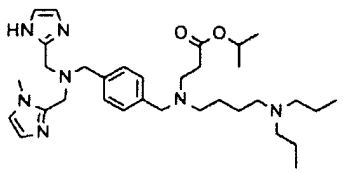
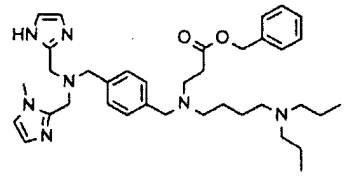
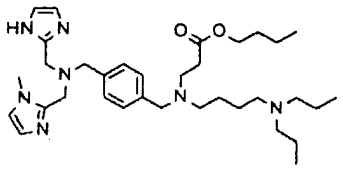
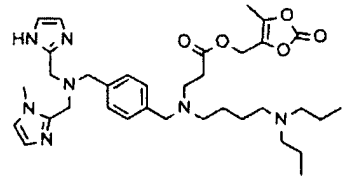
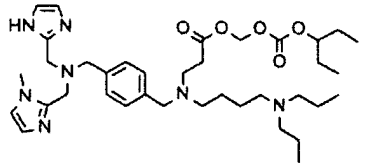
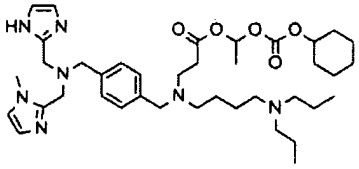
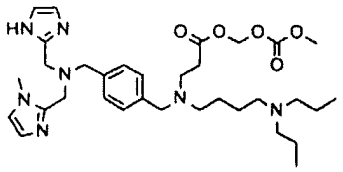
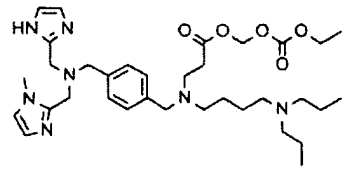
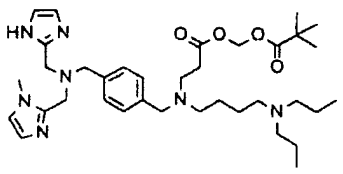
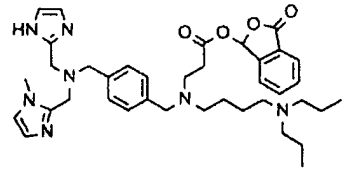
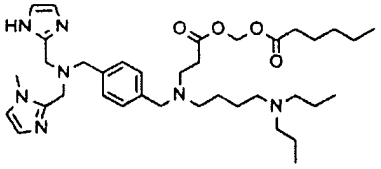
[0124]

No.	Structural Formula	No.	Structural Formula
37		38	
39		40	
41		42	
43		44	
45		46	
47		48	

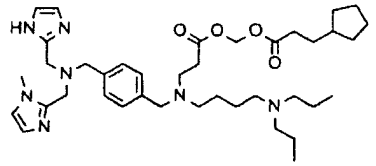
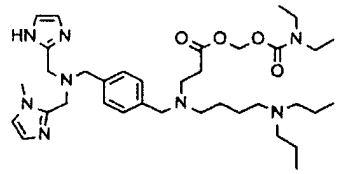
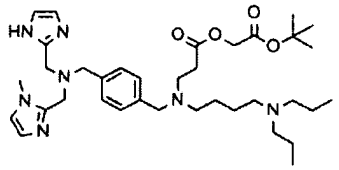
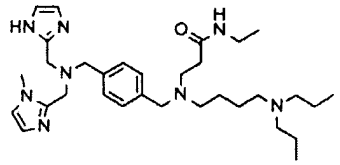
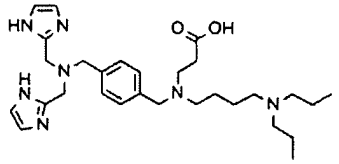
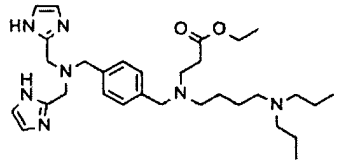
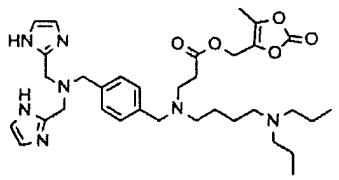
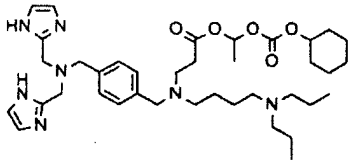
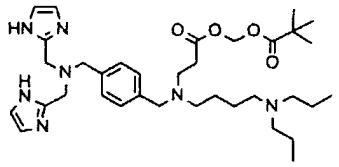
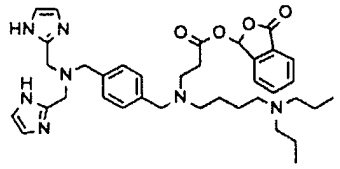
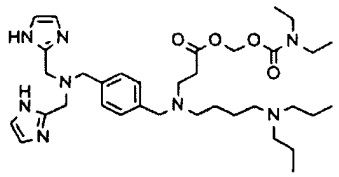
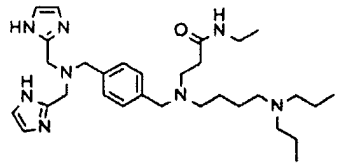
[0125]

No.	Structural Formula	No.	Structural Formula
49		50	
51		52	
53		54	
55			

[0126]

No.	Structural Formula	No.	Structural Formula
56		57	
58		59	
60		61	
62		63	
64		65	
66		67	

[0127]

No.	Structural Formula	No.	Structural Formula
68		69	
70		71	
72		73	
74		75	
76		77	
78		79	

[0128]

Next, results of activity tests and the like for the compound of the present invention are described.

[Test Example 1]

[0129]

Immediately after infection, HIV-1_{IIIB} infected MT-4 cells (3.0×10^4/well, MOI (Multiplicity of infection): 0.01) were added to a 96-well microtiter plate together with the test compounds having different concentrations. The cells were cultured in a carbon dioxide incubator at 37°C for 5 days, and the number of living cells was measured in accordance with the MTT (tetrazolium) method (Pawels, et al., J. of Virol. Method, 20, 309-321 (1998)). The antiviral activity is represented by the concentration required for inhibition of cell disorder due to HIV infection by 50% (EC_{50}: 50% Effective Concentration) (μM), and the results are shown in Table 2.

[0130]

[Table 2]

Compound No.	EC50[μM]	Compound No.	EC50[μM]
1	0.003	26	0.073
3	0.003	27	0.23
4	0.003	29	0.061
5	0.009	30	0.092
10	0.009	31	0.074
13	0.003	33	0.003
14	0.006	34	0.003
15	0.006	35	0.007
16	0.003	36	0.656
17	0.003	37	0.003
20	0.004	44	0.002
21	0.046	46	0.017
22	0.106	47	0.002
23	0.003	50	0.04
24	0.095	51	0.002

[Test Example 2]

[0131]

MT-4 cells (5×10^6/0.2 ml/well) were cultured on a 24-well microtiter plate. After the cells were incubated for 24 hours at 37°C in a carbon dioxide gas incubator, a culture medium was replaced with a buffer solution (0.1% BSA-containing RPMI-1640). Together with a ligand ^{125}I-SDF-1α (specific activity: 2,200 Ci/mmol; available from Daiichi Pure Chemicals Co., Ltd. (Tokyo)), test materials with various concentrations were subjected to a binding reaction for 2 hours under ice-cooling. Ligands that did not bind in cold PBS were washed out, and then the radioactivities of bound ligands were measured with a scintillation counter (available from Japan Packard (Tokyo)). Then, a rate of inhibition of the binding between radioactive

ligands and receptors CXCR4 by a test material was calculated (a binding-inhibition % at 0.1 μM).

The results are shown in Table 3.

[0132]

[Table 3]

Compound No.	Inhibition rate (%)
23	100

[Test Example 3]

[0133]

The aforementioned compound was examined for acute toxicity. Specifically, 6-week-old SD mice (male) were divided into several groups (2 to 3 mice in each group). Subsequently, each of the compounds of Examples was dissolved in a physiological saline solution, and the solution was transvenously administered to the mice (dose: 2.5 mg/kg) once. Then, the number of dead mice was counted. The results are shown in Table 4.

As shown in Table 4, Test Example 3 confirmed that the administration of each compound did not cause any death and the compounds id not have acute toxicity.

[0134]

[Table 4]

Compound No.	Dead mice/ test mice	Compound No.	Dead mice/ test mice
1	0/3	26	0/3
3	0/3	27	0/3
4	0/3	29	0/3
5	0/3	30	0/3
10	0/3	31	0/3
13	0/3	33	0/3
14	0/3	34	0/3
15	0/3	35	0/3
16	0/3	36	0/3
17	0/3	37	0/3
20	0/3	44	0/3
21	0/3	46	0/3
22	0/3	47	0/3
23	0/3	50	0/3
24	0/3	51	0/3

[Test Example 4]

[0135]

34.6% of the Compound No. 4, 34.6% of lactose (Japanese Pharmacopoeia; hereinafter, referred to as "(JP)"), 17.3% of corn starch (JP), 7.3% of hydroxypropylcellulose (JP), and 6.2% of low-substitution hydroxypropylcellulose (JP) were sieved and mixed well in a plastic bag. Purified water (JP) in an amount equal to those compounds was added to the mixture, and then a wet cake was obtained by kneading the mixture for 20 minutes with a biaxial kneader. The wet cake was granulated by using an extrusion granulating machine (diameter of cylindrical aperture: 1 mm), and then the granulated product was dried by using a fluidized-bed dryer (40°C, 30 minutes). The dried granules were sieved. Subsequently, magnesium stearate was added to the sieved

product in the proportion of 1% of magnesium stearate to 99% of sieved product and then the whole was mixed well, followed by making tablets having an average weight of 292 mg by means of a tableting machine.

In addition, an undercoat solution was prepared by dissolving 8% of hydroxypropylmethylcellulose (JP) and 1.6% of macrogol 6000 (JP) in purified water (JP) so as to be 100% in total. An under coat tablet was prepared by: spraying the undercoat solution using a hicoater in a ratio of 5% with respect to the weight of the tablet which was previously made; and subjecting the sprayed tablet to drying for 20 minutes.

[0136]

Subsequently, an enteric coating solution was prepared by dissolving 10% of hydroxypropylcellulose acetate succinate (Pharmaceutical excipient standards), 3% of triethyl citrate (JP), 2% of titanium oxide (JP), and 0.05% of hydroxypropylcellulose (JP) in purified water (JP) so as to be 100% in total. The enteric coating solution was sprayed by using a hicoater in a ratio of 10% with respect to the tablet weight. After the spraying, the tablet was dried for 30 minutes, thereby an enteric tablet was prepared. This enteric tablet had properties of not allowing a main component to be eluted within 2 hours in first liquid (JP), and allowing 80% or more of the main component to be eluted within 30 minutes in second liquids (JP).

[Document Name] Abstract

[Abstract]

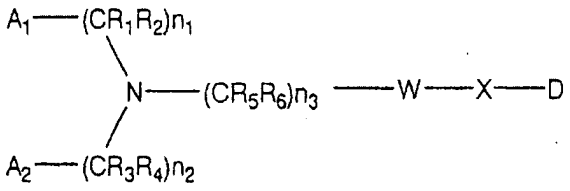
[Problems]

To probide novel amine compounds efficacious against diseases such as a viral infectious disease with HIV, rheumatism, and cancer metastasis

[Means for solving the Problems]

Amine compounds represented by the following formula (1);

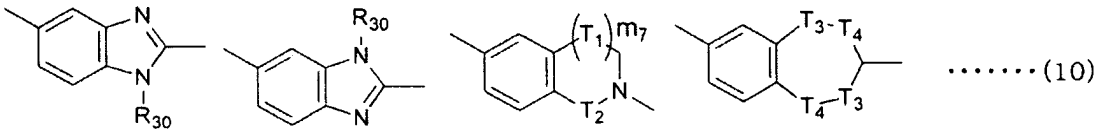
[Formula 1]



.....(1)

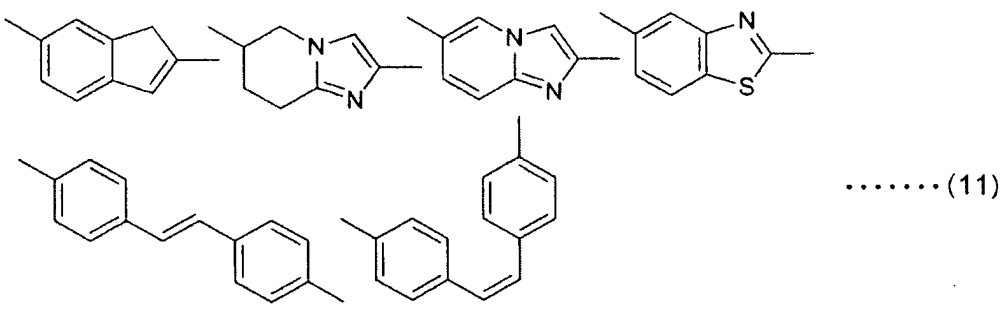
typically, A_1 and A_2 represent a hydrogen atom or a substitutable monocyclic or polycyclic heteroaromatic ring and W represents a substitutable benzene ring or any group represented by the following formula (10) or (11):

[Formula 2]



.....(10)

[Formula 3]

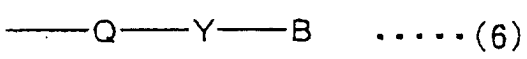


.....(11)

where

X represents O, CH_2, C(=O), NR_{11}, and D represents a group represented by the following formula (6):

[Formula 4]



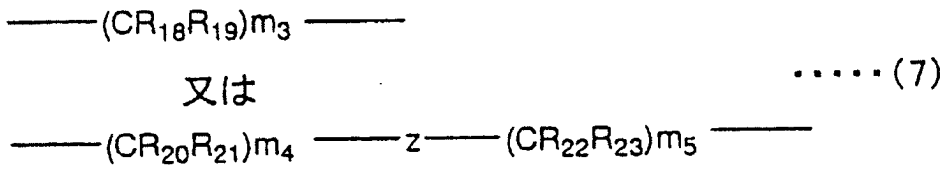
where

Q represents a single bond, NR_{12}, or a group represented by the formula (13):

[Formula 5]

and Y represents a group represented by the following formula (7):

[Formula 6]



where

z represents a substitutable monocyclic or polycyclic aromatic ring; and

B represents $-NR_{25}R_{26}$; and R_1 to R_{26} in the above formulae represent a hydrogen atom, an alkyl group, an alkenyl group, or an alkynyl group.